

Cardiac function before and after treatment for various types of loading conditions and in myocardial restriction

**A prospective study on pediatric patients with two- and three-dimensional echocardiography
and measurement of serum natriuretic peptides**

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Academic dissertation

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ABSTRACT

BACKGROUND: The incidence of all forms of congenital heart defects is 0.75%. For patients with congenital heart defects, life-expectancy has improved with new treatment modalities. Structural heart defects may require surgical or catheter treatment which may be corrective or palliative. Even those with corrective therapy need regular follow-up due to residual lesions, late sequelae, and possible complications after interventions.

AIMS: The aim of this thesis was to evaluate cardiac function before and after treatment for volume overload of the right ventricle (RV) caused by atrial septal defect (ASD), volume overload of the left ventricle (LV) caused by patent ductus arteriosus (PDA), and pressure overload of the LV caused by coarctation of the aorta (CoA), and to evaluate cardiac function in patients with Mulibrey nanism.

METHODS: In Study **I**, of the 24 children with ASD, 7 underwent surgical correction and 17 percutaneous occlusion of ASD. Study **II** had 33 patients with PDA undergoing percutaneous occlusion. In Study **III**, 28 patients with CoA underwent either surgical correction or percutaneous balloon dilatation of CoA. Study **IV** comprised 26 children with Mulibrey nanism. A total of 76 healthy voluntary children were examined as a control group. In each study, controls were matched to patients. All patients and controls underwent clinical cardiovascular examinations, two-dimensional (2D) and three-dimensional (3D) echocardiographic examinations, and blood sampling for measurement of natriuretic peptides prior to the intervention and twice or three times thereafter. Control children were examined once by 2D and 3D echocardiography. M-mode echocardiography was performed from the parasternal long axis view directed by 2D echocardiography. The left atrium-to-aorta (LA/Ao) ratio was calculated as an index of LA size. The end-diastolic and end-systolic dimensions of LV as well as the end-diastolic thicknesses of the interventricular septum and LV posterior wall were measured. LV volumes, and the fractional shortening (FS) and ejection fraction (EF) as indices of contractility were then calculated, and the z scores of LV dimensions determined. Diastolic function of LV was estimated from the mitral inflow signal obtained by Doppler echocardiography. In three-dimensional echocardiography, time-volume curves were used to determine end-diastolic and end-systolic volumes, stroke volume, and EF. Diastolic and systolic function of LV was estimated from the calculated first derivatives of these curves.

RESULTS: (I): In all children with ASD, during the one-year follow-up, the z score of the RV end-diastolic diameter decreased and that of LV increased. However, dilatation of RV did not resolve entirely during the follow-up in either treatment group. In addition, the size of LV increased more slowly in the surgical subgroup but reached control levels in both groups. Concentrations of natriuretic peptides in patients treated percutaneously increased during the first month after ASD closure and normalized thereafter, but in patients treated surgically, they remained higher than in controls. **(II):** In the PDA group, at baseline, the end-diastolic diameter of LV measured over 2SD in 5 of 33 patients. The median N-terminal pro-brain natriuretic peptide (proBNP) concentration before closure measured 72 ng/l in the control group and 141 ng/l in the PDA group ($P = 0.001$) and 6 months after closure measured 78.5 ng/l ($P = \text{NS}$). Patients differed from control subjects in indices of LV diastolic and systolic function at baseline, but by the end of follow-up, all these differences had disappeared. Even in the subgroup of patients with normal-sized LV at baseline, the LV end-diastolic volume decreased significantly during follow-up. **(III):** Before repair, the size and wall thickness of LV were higher in patients with CoA than in controls. Systolic blood pressure measured a median 123 mm Hg in patients before repair ($P < 0.001$) and 103 mm Hg one year thereafter, and 101 mm Hg in controls. The diameter of the coarctation segment measured a median 3.0 mm at baseline, and 7.9 at the 12-month ($P = 0.006$) follow-up. Thicknesses of the interventricular septum and posterior wall of the LV decreased after repair but increased to the initial level one year thereafter. The velocity time integrals of mitral inflow increased, but no changes were evident in LV dimensions or contractility. During follow-up, serum levels of natriuretic peptides decreased correlating with diastolic and systolic indices of LV function in 2D

and 3D echocardiography. **(IV):** In 2D echocardiography, the interventricular septum and LV posterior wall were thicker, and velocity time integrals of mitral inflow shorter in patients with Mulibrey nanism than in controls. In 3D echocardiography, LV end-diastolic volume measured a median 51.9 (range 33.3 to 73.4) ml/m² in patients and 59.7 (range 37.6 to 87.6) ml/m² in controls ($P = 0.040$), and serum levels of ANPN and proBNP a median 0.54 (range 0.04 to 4.7) nmol/l and 289 (range 18 to 9170) ng/l, in patients and 0.28 (range 0.09 to 0.72) nmol/l ($P < 0.001$) and 54 (range 26 to 139) ng/l ($P < 0.001$) in controls. They correlated with several indices of diastolic LV function.

CONCLUSIONS (I): During the one-year follow-up after the ASD closure, RV size decreased but did not normalize in all patients. The size of the LV normalized after ASD closure but the increase in LV size was slower in patients treated surgically than in those treated with the percutaneous technique. Serum levels of ANPN and proBNP were elevated prior to ASD closure but decreased thereafter to control levels in patients treated with the percutaneous technique but not in those treated surgically. **(II):** Changes in LV volume and function caused by PDA disappeared by 6 months after percutaneous closure. Even the children with normal-sized LV benefited from the procedure. **(III):** After repair of CoA, the RV size and the velocity time integrals of mitral inflow increased, and serum levels of natriuretic peptides decreased. Patients need close follow-up, despite cessation of LV pressure overload, since LV hypertrophy persisted even in normotensive patients with normal growth of the coarctation segment. **(IV):** In children with Mulibrey nanism, the LV wall was hypertrophied, with myocardial restriction and impairment of LV function. Significant correlations appeared between indices of LV function, size of the left atrium, and levels of natriuretic peptides, indicating that measurement of serum levels of natriuretic peptides can be used in the clinical follow-up of this patient group despite its dependence on loading conditions.

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1. LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles, referred to in the text by their Roman numerals.

- I.** Eerola A, Pihkala JI, Boldt T, Mattila IP, Poutanen T, Jokinen E: Hemodynamic improvement is faster after percutaneous ASD closure than after surgery. *Catheter Cardiovasc Interv.* 69:432-41, 2007.
- II.** Eerola A, Jokinen E, Boldt T, Pihkala JI. The influence of percutaneous closure of patent ductus arteriosus on left ventricular size and function. A prospective study using two- and three-dimensional echocardiography and measurements of serum natriuretic peptides. *J Am Coll Cardiol* 47: 1060-1066, 2006.
- III.** Eerola A, Jokinen E, Boldt T, Mattila IP, Pihkala JI. Left ventricular hypertrophy persists after successful treatment for coarctation of the aorta. The *Scandinavian Cardiovascular Journal*, in press
- IV.** Eerola A, Pihkala JI, Boldt T, Lipsanen-Nyman M, Karlberg N, Jokinen E. Cardiac dysfunction in children with Mulibrey nanism. *Pediatric Cardiology*, in press

In addition, some previously unpublished data are presented.

2. ABBREVIATIONS

2D = two-dimensional

3D = three-dimensional

A = atrial peak flow velocity

ANP = atrial natriuretic peptide

ANPN = N-terminal proatriopeptide

Ao = aorta

ASD = atrial septal defect of secundum type

Avti = velocity time integral of atrial/late mitral flow

BNP = brain/ B-type natriuretic peptide

BSA = body surface area

CNP = C-type natriuretic peptide

CoA = coarctation of the aorta

CP = constrictive pericarditis

CT = computed tomography

DT = deceleration time of the early mitral peak flow velocity

E = early mitral peak flow velocity

E/A ratio = early mitral to atrial peak flow velocity ratio

ECG = electrocardiography

EF = ejection fraction

Evti = velocity time integral of early mitral flow

f = female

FS = fractional shortening

HR = heart rate

IVSED = z score of the end-diastolic thickness of interventricular septum

LA = left atrium

LV = left ventricle/ left ventricular

LVEDD = z score of the end-diastolic diameter of the left ventricle

LVEDV = end-diastolic volume of left ventricle adjusted to body surface area measured by 2D

LVEDV3D = end- diastolic volume of left ventricle adjusted to body surface area measured by 3D

LVESV = end-systolic volume of left ventricle adjusted to body surface area measured by 2D

LVESV3D = end- systolic volume of left ventricle adjusted to body surface area measured by 3D

LVPWED = z score of the end-diastolic thickness of left ventricular posterior wall

m = male

mo = month/ months

MRI = magnetic resonance imaging

MUL = Mulibrey nanism, *muscle-liver-brain-eye*

N = number

NYHA = New York Heart Association

PDA = patent ductus arteriosus

PER = peak ejection rate

PFR = peak filling rate

PH = pulmonary hypertension

proBNP = N-terminal pro-brain natriuretic peptide

Qp/Qs = pulmonary blood flow to system blood flow ratio

RAAS = renin-angiotensin-aldosterone system

RCM = restrictive cardiomyopathy

reCoA = recurrent of coarctation of the aorta

RV = right ventricle/ right ventricular

RVEDD= z score of the end-diastolic diameter of right ventricle

SD = standard deviation

TEE = transesophageal echocardiography

TPFR = time to peak filling rate

vti = velocity time integral

y = year/ years

3. INTRODUCTION

The incidence of moderate and severe forms of congenital heart defects is 0.6%, and that of all forms, 0.75% (Hoffman and Kaplan 2002). The true incidence of congenital heart defects has not changed, although diagnosed incidence has increased, mainly because of the increased use of echocardiography (Hoffman and Kaplan 2002). Of all congenital heart defects, ventricular septal defect is the most common (20%), followed by patent ductus arteriosus (PDA) (14%), atrial septal defect (ASD) (10%), atrioventricular septal defect (7%), and coarctation of the aorta (CoA) (4%) (McCrindle 2004). Life-expectancy of patients with congenital heart defects has improved with new treatment modalities.

The first successful ligation of PDA performed through thoracotomy was reported almost 70 years ago (Gross and Hubbard 1939), and successful repair of ASD was first described more than 50 years ago (Gibbon 1954). The era of percutaneous treatment of congenital heart defect began in 1966 when William Rashkind introduced septostomy (Rashkind and Miller 1966). The first interventional closure of PDA was performed 40 years ago (Porstmann et al. 1967).

Before the surgical era, by the end of the second decade, mortality for PDA was 8.8%, for ASD 12%, for CoA 26.5%, but in normal subjects only 1.4% (Campbell 1968, 1970a, b). Early mortality has been reduced during recent decades, and the overall survival of patients with heart defects corrected surgically during childhood is as good as that of the general population (Niemenen et al. 2001, Eskedal et al. 2005).

Most congenital heart defects are of multifactorial origin. Patients with structural heart defects may require surgical or catheter treatment which may be corrective or palliative. Even those with corrective therapy need, however, regular follow-up due to residual lesions, late sequelae, and possible complications after interventions.

Development and progression of heart failure is influenced by hemodynamic, neurohumoral, cellular, and genetic factors (Auslender 2000), and among the methods to detect and to evaluate heart failure, none is ideal. In addition to clinical examination, electrocardiography (ECG), and chest X-ray, more sophisticated methods are useful to assess cardiac function. The goal is to find an accurate method of detecting the first signs of cardiac dysfunction. Catheterization is the gold standard for evaluation of cardiac structures and hemodynamics. Echocardiography with M-mode,

two-dimensional (2D), and Doppler measurements has evolved during recent decades (Frommelt 2005). Tissue Doppler is a method of evaluation of cardiac function less load-dependent than is Doppler flow measurement (Abali et al. 2005), and tissue doppler and three-dimensional (3D) echocardiography are new and more accurate tools for evaluation of cardiac function and cardiac anatomy in congenital heart defects before and after interventions. Three-dimensional echocardiography allows us to evaluate diastolic and systolic cardiac function independently of loading conditions, with a wide range of image planes (Lange et al. 2001, Marx and Sherwood 2002, Houck et al. 2005, Kapetanakis et al. 2005).

Natriuretic peptides have been studied since the 1980s. With measurement of plasma levels of brain natriuretic peptide (BNP) it is possible to differentiate cardiac from pulmonary causes of dyspnea in children (Koulouri et al. 2004) and adults (Dao et al. 2001). These peptides can be used in evaluation of heart failure (Ohuchi et al. 2003).

The timing of treatment of congenital heart defect is based on the hemodynamic and anatomic situation, with consideration of myocardial cell adaptation and chamber remodeling. It is therefore important to have multiple methods available for follow-up, and important to detect abnormalities in both diastolic and systolic left ventricular (LV) function. The aims of the therapy are to prevent and reduce LV hypertrophy, to reduce afterload, and to reduce LV filling pressure without any decrease in cardiac output (Ruzumna et al. 1996). Combinations of new imaging modalities and measurement of serum levels of natriuretic peptides may allow us to improve evaluation of cardiac function and timing of interventions.

The aim of this study was to examine prospectively the effect on LV function of different types of loading conditions caused by congenital heart defects. We evaluated cardiac function by 2D and 3D echocardiography and measured serum levels of natriuretic peptides before and after closure of ASD, occlusion of PDA, correction of CoA, and during the follow-up of patients with Mulibrey nanism.

4. REVIEW OF THE LITERATURE

4.1. Cardiac pump function

The right atrium is a distensible chamber. The right ventricle (RV) is a low-pressure volume pump. The left ventricle is a high-pressure pump with a thick muscle wall. Pressure and volume overload induces a compensatory mechanism: Concentric hypertrophy is due to increased systolic pressure with parallel replication of sarcomeres causing wall thickening, whereas eccentric hypertrophy is due to increased end-diastolic stress causing a series of replication of sarcomeres and chamber enlargement (Carabello 2002, Opie et al. 2006).

The heart consists of striated muscle, fibro-elastic connective tissue, and adipose connective tissue, and of epithelial cells. Myocytes are generally single-nucleated cells, the basic contractile unit of which is a sarcomere containing thin and thick filaments. The thick filaments contain myosin, whereas thin filaments contain actin, tropomyosin, and troponin complex (Klabunde 2005a). Organ blood flow is determined by the arterial minus the venous pressure divided by the vascular resistance of the organ, with vascular resistance determined by the size of blood vessels, arrangement of vascular network, and viscosity of the blood flowing within the vasculature (Klabunde 2005c). In heart failure, the interaction between inotropic and lusitropic properties of the heart are altered. Relaxation is more sensitive to any energy deficit than is contraction (Auslender 2000).

4.1.1. Systolic function

Cardiac systole, i.e., ventricular contraction, is initiated by electrical depolarization of the ventricles. Ventricular ejection begins when ventricular pressure exceeds the pressure within the outflow tract and continues until ventricular relaxation causes the ventricular pressure to fall and to cause the semilunar valves to close. Most cellular mechanisms regulating contraction affect calcium handling by the cell and myosin adenosine triphosphatase activity (Klabunde 2005a). Preload, afterload, and contractility are determinants of LV systolic function. Cardiac output is the product of stroke volume and heart rate. Increases in preload and contractility cause an increase, and an increase in afterload causes a decrease in stroke volume. Heart rate has an influence on stroke volume through its influence on diastolic filling time and diastolic relaxation (Hart et al. 2004). Cardiac output is normally more influenced by changes in heart rate than by changes in stroke volume. Ventricular

preload is related to the extent of ventricular filling, which can be increased by increased blood volume, augmented venous return, decreased venous compliance, atrial contraction force, and decreased heart rate. Inotropy, is regulated by autonomic nerves, circulating catecholamines, afterload, and heart rate, is the property of a cardiac myocyte that enables it to alter its tension development independent of changes in preload length (Klabunde 2005b).

Systolic dysfunction

Systolic heart failure, characterized by a loss of intrinsic inotropy, causes systemic hypoperfusion, manifested by decreased activation of mechanoreceptors in the LV, carotid sinus, and aortic arch. This leads to activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system, and release of endothelin and vasopressin. This pathophysiologic process is known as neurohumoral activation. It raises increase systemic vascular resistance, causes retention of sodium and fluid, and gradually causes myocardial fibrosis and apoptosis (Jefferies and Chang 2005).

The increase in baseline discharge from the sympathetic nervous system / RAAS together with the changes in afterload and wall stress promotes myocardial cell growth and adaptation. Continuous exposure to increased stimulation of the sympathetic nervous system has adverse effects: Myocardial oxygen consumption increases, ventricular afterload increases due to hypertrophy, interstitial fibrosis increases, capillary density decreases, and changes occur in the cytoplasmic reticulum and contractile proteins. Progressive heart failure induces the re-expression of a fetal gene program in cardiac cells. Continuous sympathetic nervous system activity leads to cardiac myocyte loss that may occur via necrosis or apoptosis. Apoptosis is an active, energy-requiring process that leads to programmed cell death and can be activated in the context of vascular remodeling, hypertension, and ischemia-reperfusion (Auslender 2000).

4.1.2. Diastolic function

During cardiac diastole, the ventricles undergo relaxation and filling. Relaxation, the first part of diastole, is an active and energy-requiring process (Labovitz and Pearson 1987, Maurer et al. 2004), and if relaxation time increases, coronary perfusion is impaired (Grossman 1991). What determines relaxation is cellular inactivation, loading conditions, and non-uniformity in the ventricle. In addition to relaxation, elastic recoil takes place during the first phase of diastole. This elastic recoil is a result of release of the energy stored in the myocardium at the end of systole as the myocardium

is compressed, becoming shorter than its equilibrium length and LV equilibrium volume (Yamamoto et al. 1996). The second phase of diastole can be divided further into three phases: early rapid-filling, diastasis, and atrial contraction. The compliance of the LV indicates the distensibility of the ventricle during filling. Myocardial stiffness differs from ventricular stiffness, which is composed of muscular stiffness and the thickness and geometry of the ventricle. It is determined primarily by myocardial characteristics (hypertrophy, ischemia, fibrosis, and infiltration) and loading conditions. Ventricular interaction, pericardial restraint, and coronary vascular engorgement additionally modify LV compliance (Glantz and Parmley 1978, Labovitz and Pearson 1987, Yamamoto et al. 1996).

Diastolic dysfunction

Extramyocardial (e.g., constrictive pericarditis) or intramyocardial (e.g., fibrosis) structural abnormalities and physiological abnormalities (e.g., impaired myocardial relaxation) of the myocardium may cause diastolic heart failure (Grossman 1990, 1991). Physiological abnormalities may be result from biomechanical changes in levels of intracellular calcium during diastole. These abnormalities may be due to dysfunction of the myocardial sarcoplasmic reticulum or changes in levels of adenosine triphosphate due to altered adenylate cyclase function induced by hypoxia. In addition, altered gene expression of ion pumps and of several proteins may lead to dysfunction (Grossman 1990, 1991). Sustained pressure overload causes increased wall stress during systole and hypertrophy of the ventricular wall. Long-term volume overload leads to increased wall stress during diastole. The LV increases in size, and cardiac myocytes increase in length and diameter—as opposed to pressure overload, in which myocytes mainly increase in diameter (Grossman 1991).

Ventricular interaction has an important influence on diastolic function; for instance changes in RV pressures and volumes can alter the filling of the LV. In addition to the RV, other external constraints of the LV filling such pericardial restraint, pulmonary characteristics and function, and coronary vascular engorgement have an influence on LV compliance (Little and Downes 1990). Normally 60 to 80% of LV filling takes place during the first third of diastole. In the disease state, the atrial booster pump serves to maintain diastolic filling (Little and Downes 1990).

4.2. Cardiac Evaluation

For cardiac evaluation, in addition to a physical examination, we can utilize ECG, chest X-ray, echocardiography, more sophisticated studies such as computed tomography (CT) or magnetic resonance imaging (MRI), and cardiac catheterization. In the physical examination, we evaluate the patient's general appearance, nutritional status, and growth. Dysmorphic features should be sought, because congenital cardiovascular anomalies are associated with syndromes and chromosomal abnormalities. Palpation of peripheral pulses and of the precordium is an important part of the examination. Blood pressure of the right arm and leg should be measured for elimination of CoA. Auscultation can evaluate heart rate and rhythm, heart sounds, and heart murmurs. Signs and symptoms of heart failure or cyanotic heart disease should be sought.

4.2.1 Clinical signs and symptoms of heart failure

Physical findings of congestive heart failure are those of 1) impaired cardiac function: tachycardia, gallop rhythm, and weak pulse, and palpation of the precordium may reveal the presence of thrill, precordial hyperactivity; those of 2) pulmonary venous congestion: tachypnea, dyspnea, retraction; and those of 3) systemic venous congestion: hepatomegaly, puffy eyelids, distended neck veins and ankle edema.

A chest X-ray makes it possible to get information about the heart's size and shape (Bardeen 1918) and may demonstrate cardiomegaly and increased vascular markings in a case of congestive heart failure. A sign of cardiomegaly is a cardiothoracic ratio of more than 0.50 for adults and 0.60 for infants.

An ECG provides information about heart rhythm, cardiac conductive properties, and atrial and ventricular hypertrophy, with findings for normal infants and children different from those of adults. RV dominance is most marked in newborns and gradually changes towards the LV dominance seen in adults. Interpretation includes rhythm, heart rate and axis, amplitude, and duration of the QRS complex and P wave. Additionally; abnormalities in Q-waves, ST-segment, and T-wave are important to see.

4.2.2. Echocardiography

The basic principle of echocardiographic imaging is the reflection of ultrasonic waves at the borders of substances with differing acoustic characteristics (e.g., density, absorption of sound waves, speed propagation). The reflected signal is detected and processed by the ultrasound receiver, and in the heart the main acoustic border is between blood and myocardium (Plein and Williams 2000).

Echocardiography has evolved since 1954 (Edler and Lindstrom 2004) and can describe anatomic abnormalities and monitor myocardial performance (Frommelt 2005). Echocardiography can utilize several modalities: two-dimensional, three-dimensional, Doppler, tissue Doppler, and M-mode echocardiography.

4.2.2.1. Two-dimensional echocardiography

Evaluation of the size of the cardiac chambers and diastolic and systolic cardiac function and detection of anatomical abnormalities is essential in the diagnostics and follow-up of congenital heart defects and in determining the indications and timing of intervention. However, estimation of LV volume and function by 2D and M-mode echocardiography is not as accurate as by angiography or MRI (Edelman et al. 1981, Mercier et al. 1982, Chuang et al. 2000). In 2D echocardiography, a single-plane and biplane area-length as well as Simpson's rule methods can be used to evaluate systolic function. The biplane Simpson method corrects for shape distortions and minimizes mathematic assumptions, but it relies on only two planes, the apex is frequently foreshortened, and data are few on normal populations. The area length method has a partial correction for shape distortion, it is based on mathematical assumptions, and normal data are few (Lang RM, et al. 2005).

4.2.2.2 Doppler echocardiography

Doppler echocardiography combines the study of cardiac structure and blood flow profiles. Pulsed and continuous wave Doppler and color flow Doppler are mostly used for measurement of blood flow velocities and calculation of pressure gradients (Vermilion 1997). Pulsed wave Doppler emits a short burst of ultrasound, whereas the continuous wave Doppler emits a constant ultrasound beam. With pulsed wave Doppler, the sample site can be controlled, but the maximal detectable velocity is limited. With continuous wave Doppler, high velocities can be measured, but sample site cannot be determined (Park 2002).

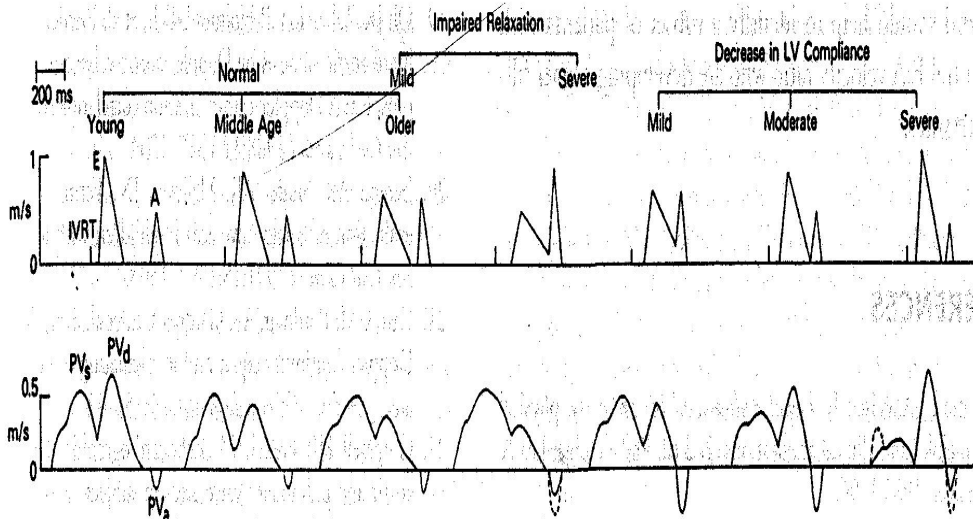
From flow measurement at the level of the tips of the mitral valve leaflets, it is possible to derive LV filling parameters and estimate the diastolic function. The early mitral peak flow velocity (E wave), deceleration time (DT) of the E wave, atrial peak flow velocity (A wave), the early mitral to atrial peak flow velocity ratio (E/A), and the duration of the A wave are parameters usually measured for the assessment of LV diastolic function. In Doppler evaluation, important factors are sample volume, recording speed, beam alignment, and placement of the sample volume, as well as echocardiography machine settings (Bryg et al. 1987, Benjamin et al. 1992, Appleton et al. 1997).

Stroke volume, heart rate, and the mitral ring area are main determinants of the velocity time integral of early ventricular filling (Evti). Peak flow velocities of atrial filling are mainly correlated with heart rate. The Evti increases from the second month of life up to 19 years of age. In the velocity time integral of the atrial ventricular filling (Avti), no significant changes occur during childhood. The E wave is stable from infancy to adolescence, but the A wave decreases significantly during infancy and childhood. The ratios of early to atrial (E/A) phase parameters and the atrial filling fraction undergo significant changes during the early years of life (O'Leary et al. 1998, Schmitz et al. 1998). During the first 3 to 6 months of age, changes occur in diastolic function towards improved relaxation and compliance of LV (Kozak-Barany et al. 2000, Schmitz et al. 2004). Doppler measurements of mitral inflow velocities have been validated by comparing them with cineangiography (Rokey et al. 1985, Pearson et al. 1988). Left ventricular peak filling rate (PFR), as estimated with radionuclide ventriculography, is dependent on age and heart rate. Doppler measurement of PFR has correlated poorly with radionuclide PFR (Miller et al. 1986).

The initial abnormality in diastolic dysfunction is loss of the elastic recoil in early diastole. In the first stage of diastolic dysfunction (abnormal relaxation pattern), there is a lower than normal early E/A ratio and prolongation of the DT of the E wave in the Doppler velocity tracing. Stage II is called the pseudonormal pattern where active myocardial relaxation has declined, and ventricular operative compliance is abnormal. In the Doppler flow curve, mitral inflow is similar to normal. As diastolic dysfunction progresses, the E wave increases, DT becomes very short, and the A wave is small. This is called the restrictive pattern and stage III of diastolic dysfunction. If this restrictive pattern persists despite manipulation of filling pressure, then it is irreversible and is called stage IV LV diastolic dysfunction (Appleton et al. 1988, Appleton et al. 1993, Yamamoto et al. 1996, Appleton et al. 1997, Ommen 2001, Ommen and Nishimura 2003, Wood and Picard 2004) (Figure 1).

Different loading conditions have effects on transmitral flow velocity curves (Wood and Picard 2004). Acute decrease in preload lowers E and A waves, and DT of the E wave increases. Increase in preload has an opposite effect. The E wave decreases and DT of E wave and the A wave increase if afterload is increased (Snider et al. 1985, Yamamoto et al. 1996).

Figure 1. Mitral inflow and pulmonary venous flow pattern in Doppler echocardiography in evaluation of LV diastolic function.



Appleton C and Hatle L., The natural history of left ventricular filling abnormalities: assessment by two-dimensional and Doppler echocardiography. *Echocardiography* 9: 437-57, 1992. With permission of Blackwell Publishing Limited.

New Doppler techniques include the tissue Doppler method, in which LV diastolic function can be assessed by measuring the velocity of cardiac muscle. Combination of measurements of Doppler flow with tissue Doppler gives more information about diastolic function (Ommen 2001). Tissue Doppler may be less load-dependent than is conventional Doppler echocardiography. A chronically increased LV afterload in the presence of a normal preload may influence the measurements despite normal diastolic function (Eidem et al. 2005).

4.2.2.3. M-mode echocardiography

M-mode echocardiography is an important tool in the evaluation of cardiac function. It is used for measurement of dimensions of the cardiac chambers and vessels and of the thicknesses of ventricular septum and free wall, evaluation of LV systolic function, and detection of pericardial fluid (Park 2002). In order to minimize interobserver variability, international guidelines for measurement of M-mode echocardiographies have been published (Sahn et al. 1978, Schiller et al. 1989, Lang et al. 2005, Lang et al. 2006). The left atrium/ aorta (LA/Ao) ratio can be calculated to estimate the size of the left atrium. Diastolic and systolic wall thicknesses and left and right ventricular dimensions can be measured by M-mode recording perpendicular to the long axis of the LV. The standard level to measure in infants and young children is at the mitral valve leaflet tips. In older children and adolescents, measurements can be done at the level of the chordae as in adults (Sahn et al. 1978). Normal values are known for infants (Hagan et al. 1973, Solinger et al. 1973) and children (Lundstrom 1974a, b, Epstein et al. 1975, Kampmann et al. 2000). Validation of M-mode measurements of aortic root diameter and the size of LA, LV and RV has been performed with angiography (Lundstrom and Mortensson 1974a, b).

Measurements can be indexed based on age, weight, height, or body surface area (BSA). The correlations of BSA with LV end-diastolic and end-systolic diameters and volumes are stronger than are those with age, weight, or height (Lester et al. 1987, Franklin et al. 1990). The normal range is given either as standard deviation (SD) or as percentiles (Henry et al. 1980, Kampmann et al. 2000). End-diastolic and systolic dimensions of LV and wall thicknesses as measured by M-mode are heart-rate dependent (DeMaria et al. 1979).

End-diastolic and systolic LV volumes measured by M-mode have a good correlation ($r = 0.97$) with those measured by angiography, with low interobserver variability in M-mode measurements (Pombo et al. 1971). In these measurements, the assumption is uniform and symmetrical LV contraction (Teichholz et al. 1976). In 2D echocardiography, the biplane Simpson method corrects for shape distortions and minimizes mathematical assumptions, but it relies on two planes only. The problem is that the apex of the heart is frequently foreshortened, and data are few on normal population (Lang et al. 2005). However, 2D echocardiography may be more accurate than M-mode echocardiography in volume measurement when compared with angiography (Silverman et al. 1980).

4.2.2.4. Three-dimensional echocardiography

Three-dimensional echocardiography has developed since the 1970s (Dekker et al. 1974, Moritz et al. 1983). It was first used to evaluate the morphology of the mitral valve (Levine et al. 1992), and improvement during the last decade, allowing today also real-time volumetric 3D echocardiography. This three-dimensional echocardiography allows use of any planes and projections in assessment of cardiac morphology and function (Marx and Sherwood 2002, Poutanen et al. 2006), this leading to improved anatomic visualization and diagnostics of morphological cardiac defects, assessment of LV function, and evaluation of regional or global wall motion at rest and during or after exercise (Roelandt 1998). Current probes, however, are not able to capture the entire cardiac volume in patients with severely enlarged hearts (Houck et al. 2005). Volume-time curves of LV allow quantitative and qualitative analysis of global and segmental LV function (Poutanen et al. 2003). Left ventricular diastolic function can be evaluated by measuring the rate and timing of LV filling (Houck et al. 2005). The systolic dyssynchrony index is used to optimize therapeutic pacing in systolic heart failure (Kapetanakis et al. 2005). The full volume of the heart can be acquired by obtaining four cardiac cycles of data. As the heart rate increases, only a limited number of frames are available for analysis due to the decreased cardiac cycle, which sometimes makes detection of true end-diastolic and systolic frames impossible (Houck et al. 2005).

End-diastolic and systolic volumes of LV measured by 3D echocardiography have been validated and compared with MRI (Gopal et al. 1993, Altmann et al. 1997, Buck et al. 1997, Iwase et al. 1997, Vogel et al. 1997, Nosir et al. 1998b, Chuang et al. 2000, Hibberd et al. 2000, Poutanen et al. 2001), and angiography (Nixon et al. 1983, Zoghbi et al. 1990, Sapin et al. 1993, Sapin et al. 1994, Kupferwasser et al. 1997, Roelandt 1998, Heusch et al. 1999). Similarly, real-time 3D echocardiography correlates with MRI in measurements of LV volumes, mass and systolic function (Jenkins et al. 2004), and with radionuclide cineangiography in the assessment of LV ejection fraction (EF) (Acar et al. 1998).

Different processing methods exist. For off-line reconstruction and analysis of 3D volumes there is a need for simultaneous registration of accurate spatial positioning and timing of the cross-sectional 2D images (Roelandt 1998). 3D echocardiography has three phases: data acquisition, postprocessing, and rendering. Acquisition requires temporal and spatial gating. Scanning can be done by parallel or linear, rotational, or fan-like method. Data collection can be random or sequential or on-line collection.

Postprocessing involves the reformatting of 2D data information. Sequentially collected 2D data are digitized and realigned according to their spatial and temporal sequences. Interpolation of data points occurs when converting the 2D data into a volumetric data set (Roelandt 1998, Marx and Sherwood 2002). Motion artifacts may be due to movement of the patient, to respiration-related movement of the heart, or to movement of the probe. After rendering, i.e., developing the 3D image, volumetric data are available, and an unlimited number of cut planes and projections can be obtained. Cutting planes can be derived by various algorithms: anyplane, paraplane, long-axis, and short-axis methods, as well as the mainplane method (Roelandt 1998). Improved standard 2D imaging will result in enhanced 3D reconstructions. The greater the number of imaging planes obtained, the better the resolution of the rendered images. In sequential imaging, an increase in the number of imaging planes increases the potential for movement artifacts. On the other hand, a better 3D image will be achieved if a greater number of 2D planes are perpendicular to the area of interest (Marx and Sherwood 2002).

With ECG and respiratory gating, measurements of LV volume in 3D echocardiography are comparable with those obtained by equilibrium radionuclide angiography (Acar et al. 1998). In 3D echocardiography, the end-diastolic and systolic volumes and EF can be calculated by several methods: polyhedral surface reconstruction (Gopal et al. 1992), Simpson's rule, the apical biplane-modified Simpson method, and an algorithm based on the analysis of long-axis views displaying dynamic reconstruction of the LV (Nosir et al. 1998a, Li and Sanders 1999, Krenning et al. 2003). Volume can be computed without the use of geometric assumptions, an advantage as compared with 2D echocardiography and cineventriculography, which both make assumptions about LV shape. Dynamic changes in LV volume during the cardiac cycle as measured by 3D echocardiography are comparable to those determined by MRI (Poutanen et al. 2001).

Real-time 3D echocardiography allows evaluation of the diastolic function of the LV with volume-time curves. Similar indices as in MRI and radionuclide angiography can be measured: PFR, peak ejection rate (PER), and time to peak filling rate (TPRF). PFR has been reduced and TPRF elongated in patients with coronary artery disease and arterial hypertension (Zeidan et al. 2002).

4.2.2.5. Inter- and intraobserver variability

Interobserver variability for 2D diameters and end-diastolic and systolic volumes has been 9% for the LV dimension (King et al. 1992) and under 5% for end-diastolic and systolic LV dimensions measured by M-mode (Silverman et al. 1980); volumes measured by modified Simpson's rule or the area length method have been 3 to 14% (Silverman et al. 1980, Kupferwasser et al. 1997, Takuma et al. 2001). Intraobserver variability for LV volume as measured by 2D echocardiography has been 3 to 12% (Silverman et al. 1980, Kupferwasser et al. 1997, Takuma et al. 2001). For M-mode measurements, intraobserver variability may be less than 5% (Silverman et al. 1980). Interobserver / intraobserver variability for LV end-diastolic volume in angiography has been 3 to 9% and 3 to 11%, respectively, and for LV systolic volume 3 to 7% and 3 to 9% (Silverman et al. 1980, Kupferwasser et al. 1997).

In 3D echocardiography, interobserver variability is due to inherent subjectivity in interpretation of 2D data (Houck et al. 2005); it may be 1 to 8% for end-diastolic and zero to 8% for end-systolic volumes (Apfel et al. 1996, Kupferwasser et al. 1997, Takuma et al. 2001). In 3D echocardiography, intraobserver variability has been measured as 2% to 10% for EF (Gopal et al. 1995, Kupferwasser et al. 1997, Acar et al. 1998, Takuma et al. 2001), 3% for LV dimensions (King et al. 1992), and 12% for LV mass (Gopal et al. 1997).

4.2.3. Catheterization

Cardiac catheterization and angiography constitute the final definitive diagnostic tests for some proportion of patients with congenital heart defects. The first cardiac catheterization was performed by Bernard in 1844 and the first human cardiac catheterization by Forssmann in 1929 (Grossman 2000). Today, cardiac catheterization is a combined hemodynamic and angiographic procedure undertaken for diagnostic and therapeutic purpose. It provides data on blood pressure and oxygen saturation and the existence and magnitude of shunts, allowing calculation of cardiac output. With pressure data, the systemic and pulmonary vascular resistance indices can be calculated and information on the site and severity of obstruction achieved (Grossman 2000).

Selective angiocardiology is usually performed as part of the catheterization procedure (Park 2002). Angiography makes it possible to visualize cardiac structures and to evaluate cardiac function. Reference data on LV volumes in adults appeared in the 1960s, and the first angiographic

studies on pediatric patients were reported more than 40 years ago (Miller et al. 1964). An increase in heart rate causes decrease in LV end-diastolic and systolic volumes and increase in the thicknesses of the interventricular septum and LV posterior wall but has no effect on LV fractional shortening (FS) or ejection fraction (Kennedy et al. 1966).

Evaluation of LV diastolic function by single-plane cineangiographic LV volume curves has shown that in normal adult patients, atrial contraction represents up to 21% of the stroke volume. In normal adults, PFR and PER closely approximate each other (Hammermeister and Warbasse 1974).

Interventional cardiac catheterization has evolved since Rashkind introduced septostomy in 1966 (Rashkind and Miller 1966). Nowadays, cardiac catheterization is not only a diagnostic but more often a therapeutic procedure (Gibbs 2000a, b).

4.2.4. Computed tomography (CT) and magnetic resonance imaging (MRI)

Computed tomography (CT) and magnetic resonance imaging (MRI) have been developed for assessment of cardiovascular structures and function. CT was taken into clinical use in 1972 and MRI in the late 1980s (Suramo 1998). The examination is more challenging in pediatric patients because of higher heart rates, smaller cardiovascular structures, and the large scope of congenital heart defects (Jelnin et al. 2006). With CT imaging it is possible to get additional information on other thoracic structures such as airways and lung parenchyma. Disadvantages include limited functional information, poorer temporal resolution, and radiation exposure (Frush and Herlong 2005).

The MRI technique provides 3D reconstructions with good resolution. Image acquisition times and protocols and quality have all improved (Frakes et al. 2005, Moore 2005, Raval and Lederman 2005). With MRI it is possible to visualize the pulmonary and systemic vasculature and achieve information about blood flow distribution and cardiac function (Ley et al. 2006).

4.2.5. Natriuretic peptides

The heart also acts as an endocrine gland. The natriuretic peptides were discovered between 1980 and 1990: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and dendroaspis natriuretic peptide, forming the natriuretic peptide system. These play an important role in regulation of fluid homeostasis and of blood pressure/ vascular tone, and in inhibition of cardiomyocyte growth. This system's function in retarding the progression of heart failure is the opposite of the effect of the neurohumoral system, such as RAAS and the sympathetic nervous system (Goetze 2004, Munagala et al. 2004, Cea 2005).

Atrial natriuretic peptide (ANP) is produced primarily in the atrial myocyte and in smaller amounts in ventricular myocytes. It appears in fetal ventricular tissue and in hypertrophied ventricles (Munagala et al. 2004, Cea 2005). It is stored as a pro-hormone in atrial granules and released in response to wall stress. In the presence of heart disease, ANP gene expression is up-regulated in ventricular myocytes. Reversion to a fetal genotype takes place, and ventricles contribute to a great amount of circulating ANP, because the number of ventricular myocytes is larger than that of the atrial. Norepinephrine, angiotensin II, endothelin, and cytokines also stimulate the production and release of ANP. The half-life of the larger, biologically inactive N-terminal fragment is 40 to 59 minutes and that of the smaller, biologically active fragment is only 2 to 5 minutes (Munagala et al. 2004).

Brain natriuretic peptide (BNP) is produced in atrial and ventricular myocytes. In healthy people, the main site of gene expression is atrial, but in disease states such as heart failure, ventricular gene expression is up-regulated (de Bold et al. 2001, Hall 2005). BNP is stored together with ANP in storage granules in the atrial myocytes in the healthy state. As the BNP gene is up-regulated in ventricular myocyte, storage is also possible (Goetze 2004, Munagala et al. 2004). BNP secretion is, however, predominantly controlled at the transcriptional level (Cea 2005). The half-life of the larger, biologically inactive N-terminal fragment (NT-BNP) is 70 minutes and that of the smaller, biologically active fragment 22 minutes. The stimulus for synthesis and release of BNP is wall stress (Goetze 2004, Munagala et al. 2004). Catecholamines and angiotensin-II, vasoactive substances, enhance BNP gene transcription and secretion (Hanford and Glembotski 1996).

Because CNP is secreted by the vascular endothelium, it is therefore not a cardiac peptide. Its key function is paracrine inhibition of vascular growth (Goetze 2004).

The action of the natriuretic peptide system is mediated by cyclic guanosine monophosphate. Production of guanylyl cyclase is stimulated by binding of natriuretic peptides to their receptors of A and B type. Natriuretic peptides are cleared from the systemic circulation by binding to the natriuretic peptide C receptor and by the neutral endopeptidases—present in the vascular endothelial cells, smooth muscle cells, renal epithelial cells, and fibroblasts (Munagala et al. 2004). The natriuretic peptide system produces vasodilatation through a direct mechanism and also by a suppressive effect on the vasoconstrictive hormonal system such as the action of endothelin and RAAS. Natriuresis and diuresis are a result of natriuretic peptide system activity in healthy humans or animals, but these effects are not clear in heart failure. The natriuretic peptide system has anti-hypertrophic and anti-fibrotic effects on cardiac structure, and in vitro studies show the natriuretic peptide system inhibiting the action of humoral stimulators which cause cardiomyocyte growth (Munagala et al. 2004).

Normal levels of ANP and BNP or their inactive N-terminal fragment have been studied by different methods (Table 1) (Weil et al. 1986, Yoshibayashi et al. 1995, Koch and Singer 2003, Mir et al. 2003, Rauh and Koch 2003, Nir et al. 2004), each method having a specific range of normal values. The levels of natriuretic peptides are higher immediately after birth and decrease thereafter during the first 2 to 4 months (Weil et al. 1986, Matsuoka et al. 1988, Nir et al. 2004). As for serum levels of natriuretic peptides between genders, studies have given controversial results (Weil et al. 1986, Redfield et al. 2002, Koch and Singer 2003, Mir et al. 2006).

Studies on levels of natriuretic peptides in pediatric patients with different types of congenital heart defects and heart failure are listed in Tables 2 and 3. Plasma ANP and BNP levels in children with cardiac defects depend on degree of heart failure (Weil et al. 1986). Elevated plasma levels of ANP and BNP in patients with ASD normalize after percutaneous closure of the defect (Muta et al. 2002). Positive correlations exist between BNP levels and left-to-right shunt, ventricular volume, and the pulmonary-to-systemic pressure ratio in high-pressure lesions. Levels are higher in patients with a high-pressure shunt than in those with a low-pressure shunt (Nir et al. 2004, Holmgren et al. 2005). In volume overload of LV caused by such problems as PDA and ventricular septal defect, BNP levels correlate with the end-diastolic volume of the LV and with pulmonary blood flow to system blood flow ratio (Q_p/Q_s). In volume overload of the RV caused for example by ASD, levels correlate with end-diastolic volume of RV and with Q_p/Q_s (Kunii et al. 2003).

ANP level correlates positively with pulmonary artery pressure and pulmonary resistance (Oberhansli et al. 1990) and decreases after treatment of a congenital cardiac defect in children older than 3 months. In newborns, the levels are normally higher, and a similar influence from therapy may not occur.

Plasma levels of BNP are useful in differentiating congestive heart failure from lung disease in children with respiratory distress (Koulouri et al. 2004), and after biventricular repair of congenital heart defects, BNP levels increase postoperatively (Sun et al. 2005).

The biological activity of ANP decreases in infants with intracardiac left-to-right shunt immediately after cardiopulmonary bypass (Seghaye et al. 1997), and ANP levels increase during cardiopulmonary bypass in adult patients undergoing a coronary artery bypass operation. The levels are higher in those operated on with hypothermia and cold cardioplegia than in those with normothermia and warm cardioplegia (Brancaccio et al. 2004).

In adult patients with differing types of cyanotic heart defects, plasma levels of ANP and BNP are higher than in healthy controls and in patients treated for acyanotic heart defects. This may be due to increased secretion of ANP and BNP in human cardiac myocytes caused by hypoxia (Cowley et al. 2004, Hopkins et al. 2004). Similarly, in animal studies, hypoxia induces ANP and BNP gene transcription (Toth et al. 1994). However, some studies have failed to demonstrate any correlation between oxygen saturation and levels of natriuretic peptides (Cowley et al. 2004).

In adult patients with chronic heart failure, elevated plasma concentrations of ANP are related to impaired LV systolic function and to restrictive filling patterns (Wijbenga et al. 1999): In adults with congenital heart disease, levels of ANP and BNP increase stepwise by New York Heart Association class (NYHA), and they increase along with decreased systemic ventricular function (Bolger et al. 2002). Plasma levels of BNP correlate with pulmonary vascular resistance and pulmonary artery pressure, and are inversely correlated with cardiac index in adult patients with primary pulmonary hypertension (PH) (Leuchte et al. 2004).

Table 1 Normal values of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) among studies

Study	Subjects Age range number	Plasma	Method	upper limit	mean	range	note
(Weil et al. 1986)	neonates 2-4 days n = 15	ANP		-	227 pg/ml	129-356 pg/ml	
	children > 1 mo -16 y n = 148			-	47 pg/ml	2-109 pg/ml	no sex-related dependence in the infants and children studied
(Yoshiyayashi et al. 1995)	0 day n = 20	ANP	RIA	-			
	0 day n = 20	BNP	RIA	-	56.7 fmol/ml	±49.6 (SD) fmol/ml	
(Mir et al. 2002)	children 1day-17 y 109	N-BNP	Biomedica	10 th and 90 th 150 and 430 fmol/ml	311 fmol/ml	74-654 fmol/ml	
	children 2 wks-17.6 y n = 152	BNP	Triage BNP	32.7 pg/ml	8 pg/ml (< 10 y) 12 pg/ml (girls > 10 y) 5 pg/ml (boys > 10 y)	-	age < 10 y; girls = boys age > 10 y; girls > boys
(Koch and Singer 2003)	neonates 1-6 days n = 43	BNP	Triage BNP	-	231.6 pg/ml (0-1 days) 48.4 pg/ml (4-6 days)	-	
	children n = 242	BNP	Shionogi RIA	-	5.3 pg/ml	-	
(Kunii et al. 2003)	neonates 1-7 days n = 11	BNP	Shionogi RIA	-	119 pg/ml (0 day) 15 pg/ml (7 days)	-	

Study	Subjects Age range number	Plasma	Method	upper limit	mean	range	note
(Mir et al. 2003)	delivery n = 51	N-BNP	Biomedica	-	221 fmol/ml	58-478 fmol/ml	
	day 1 n = 18	N-BNP		-	641 fmol/ml	254-1272 fmol/ml	
	day 3 n = 16			-	246 fmol/ml	110-430 fmol/ml	
	neonates delivery n = 51	N-ANP	Biomedica	-	5680 fmol/ml	1005-16900 fmol/ml	
	day 1 n = 18	N-ANP		-	96 700 fmol/l	6912-436000 fmol/ml	
(Rauh and Koch 2003)	day 5 n = 16			-	5232 fmol/ml	2691-7353 fmol/ml	
	neonates 1 day-1 mo n = 13	NT- ProBNP	Elecsys system	-		1121-7740 pg/ml	
	children 4mo-18 y n = 78	NT- ProBNP	Elecsys system	299pg/ml (97.5 th percentile age 1 y) 48pg/ml (97.5 th percentile age 16 y)	83.4 ng/l	11-379 ng/l	levels decrease with age
	neonates 1-5 days n = 20	NT- ProBNP	Elecsys system		1937 pg/ml	28-5309 pg/ml	
	children 4mo-15 y n = 58	NT- ProBNP	Elecsys system	348.6pg/ml (95 th percentile)	111 pg/ml	5-391 pg/ml	no correlation with age

ANPN = N terminal pro-atrial natriuretic peptide
BNP = brain/ B-type natriuretic peptide; NT-proBNP = N-terminal segment of BNP pro-hormone; N-BNP = N-terminal pro-brain natriuretic peptide; mo = month; wks = weeks; y = years;

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Elecsys system = An electrochemiluminescence immunoassay; Roche diagnostic Corporation, Mannheim, Germany

Biomedica = A competitive Enzyme Immunoassay; Biomedica, Vienna, Austria

Table 2. Plasma levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) in different cardiac defects; studies not including follow-up.

Study	Subjects Age median (range)	number of patients with dg	Method	Patients ANP median (range)	Patients BNP median (range)	N and age of controls median (range)	controls ANP	controls BNP	difference P value as compared with controls
(Weil et al. 1986)	Children mean 5.2 y (3 mo-14.5 y)	cor pulmonale (4), TA (3), TOF (7), AVSD (5), VSD (7), ASD (6), heart failure due to Cm (8), AV fistula, PDA,EF(2), CoA+PDATGA+PD A, TGA st.p Mustard+TI,	RIA	284 (93-967) pg/ml HF+; 57 (15-118) pg/ml HF-	-	-	-	-	-
(Kikuchi et al. 1987)	children 6 (1-16) y 2 (1-3) y	ASD (13) PDA (5)	RIA	mean±SD 99.4 ± 40.7 pg/ml (range 50.0-180.6) mean±SD 116.3 ± 26.5; (range 88.6- 151.2) pg/ml HF- (n=4); 416.0 pg/ml HF+	-	n = 30 4 (12 day- 15) y	mean±SD 44.6 ± 22.3 pg/ml range 11.7- 98.7	-	< 0.001 < 0.001
(Matsuoka et al. 1988)	children 2 mo-14 y	ASD (7) PDA (6) VSD (18)	RIA	mean±SD 65 ± 42 pg/ml mean±SD 124 ± 38 pg/ml mean±SD 221 ± 123 pg/ml	-	n = 53 1 mo- 15 y	< 80 pg/ml	-	- - -

Study	Subjects Age median (range)	number of patients with dg	Method	Patients ANP median (range)	Patients BNP median (range)	N and age of controls median (range)	controls ANP mean	controls BNP mean	difference P value as compared with controls
(Iivainen et al. 2000)	adults 43 (17-71) y	ASD (65)	IRMA	mean 0.41± 0.32 nmol/l, median 0.31 nmol/l	-	n = 67 42 (22-68) y	mean 0.24± 0.12, median 0.23 nmol/l	-	0.0003
(Mir et al. 2002)	Children mean 13 mo (1mo-14 y) mean 13 mo (1mo-14 y)	DCM(14), HLHS (4), TOF postop (2), MR (1) VSD (7), AVSD (3)	Biomedica		mean 761 (219-2008) fmol/ml mean 1022 (386-2718) fmol/ml	n = 109 (11 days- 17 y)		mean 311 (74-654) fmol/ml	31 children with HF p < 0.05
(Kunii et al. 2003)	children 69 ± 8.5 mo 37.5 ± 6.4 mo 41.2 ± 4.6 mo	ASD (34) PDA (29) VSD (91)	Shionoria		37.6±8.4 pg/ml 32.8±6.5 pg/ml 46.1±7.3 pg/ml	n = 242 (1 mo-16 y)	-	5.3 ± 3.8 pg/ml	-
(Wahlander et al. 2003)	children (0.5-0.7) y 1.8-3.7 y	UVH 1 st palliative oper (7) UVH Glenn (19)	Shionoria	mean 103 (17-203) ng/l mean 29 (16-54) ng/l	mean 52.8 (8.3- 122) ng/l mean 7.3 (0-16) ng/l	n = 14 (0.1-4.5) y	mean 32 (12-52) ng/l	mean 5.9 (0-13.8) ng/l	

Study	Subjects Age median (range)	number of patients with dg	Method	Patients ANP median (range)	Patients BNP median (range)	N and age of controls median (range)	controls ANP ng/l	controls BNP ng/l	difference P value as compared with controls
(Westerlind et al. 2004)	4.5 (0.3-16.2) y	CoA (9)	Shionoria	42.2 (13.7-63.2) ng/l	7 (4.8-24.4) ng/l				
	0.4 (0.3-4.5) y	VSD (11)		166 (31.8-346) ng/l	30.8 (10.7-81.5) ng/l				
	3.4 (0.3-14.8) y	DCM (6)		412 (148-553) ng/l	638.5 (263-1300) ng/l				
	Children 6.8 (0.3-16.2) y	AS(8), CoA(7)	Shionoria	40.8 (12.6-210) ng/l	6.8 (0.7-170) ng/l	n = 23 1.1 (0.1-8.3) y	4.7 (0.0-17.7) ng/l	32.9 (11.7-212.1) ng/l	
(Leyva et al. 2005)	1.9 (0.3-14.7) y	PS (5), Trunc (3), PA+VSD(2), TGA+PS(1)		69.3 (8.7-182) ng/l	18.0 (5.0-29.1) ng/l				
	0.5 (0.3-4.9) y	VSD(13), PDA(3)		164 (31.8-346) ng/l	55.4 (10.7-352) ng/l				
	4.0 (9.5-13.3) y	ASD(16), ASDpr(2), PAPVR(1)		57.2 (11.3-234.1) ng/l	15.6 (0.0-105.1) ng/l				
	47-81 y	CP (6)	ADVIA	-	143 (50-186) pg/ml				
(Mir et al. 2005)	24-73 y	RCMP (5)		-	756 (639-1060) pg/ml				
	Children mean 4.77 (0.2-17.3) y	post op: PS (11), PA (8); preop: ASD (7); TAPV (5)	Triage	-	87.7 (5-316) pg/ml				

ANPN = N terminal pro-atrial natriuretic peptide, AS = stenosis of the aortic valve, ASD = atrial septal defect of secundum type, ASDpr = atrial septal defect of primum type, BNP = brain/ B-type natriuretic peptide, CoA = coarctation of the aorta, CP= constrictive pericarditis, DCM = dilated cardiomyopathy, EF = endocardial fibroelastosis, HF = heart failure, mo = month/ months, IRMA = immunoradiometric assay, PAPVR = partial anomalous pulmonary venous return, PDA = patent ductus arteriosus, PS = stenosis of the pulmonary valve, RCMP = restrictive cardiomyopathy, RIA = radioimmunoassay, TGA = transposition of great arteries, TI = tricuspid insufficiency, Trunc = truncus arteriosus with conduit stenosis, VSD = ventricular septal defect, y = year/ years

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ADVIA Centaus system, Bayer, Tarrytown, New York: immunoassay

Table 3. Levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) measured in studies with a follow-up.

Study	Subjects/ Age (range)	diagnosis/ (number of patients)	Method	N controls	controls mean (range)	patients mean(range) before	P value compared with controls	follow- up time	mean(range) after intervention	P value compared with baseline/ controls
(Zeevi et al. 1998)	Children/ over 3 mo Newborns	PS(8), AS(4), PDA(6), CoA(3), MS(1) PS(3), AS(1), TGA(2)	plasma ANP	9	24.6± 4.6(SEM) pg/ml	125.2 ± 15.8(SEM) pg/ml	< 0.0001	7-30 days	42.9 ± 5.0	P < 0.0001/ P < 0.02
				7	220.8± 16.2(SEM) pg/ml	243.0 ± 42.1 (SEM)pg/ml	NS	7-30 days	62.1 ± 12.7	P < 0.005 with baseline
(Muta et al. 2002)	children/ 6-17y	ASD(14)	Shionogi RIA ANP	10	17 ± 6.8 ng/l	24 ± 9.8 ng/l	< 0.05		34 ± 18 ng/l 5min < 0.05	
					12 ± 4.9 ng/l	19 ± 9.9ng/l	< 0.05		19±11 24 h NSs 23±14 ng/l 5min <0.05 32 ± 11 ng/l 24 h < 0.05 12 ± 6.3 ng/l 3 mo P = NS	
(Cowley et al. 2004)	children and adults/ 1day -19 y	n=107; 11 >19 y: PS(10), TOF(9), ASD(9), PDA(9), AS(8), CoA (9), UVH(6), PA+VSD(5), SAS(4) ASD (3)	Triage BNP			median 19.0 (<5.0- >1300.0) pg/ml				
(Erbay et al. 2004)	2-17.7y adults/ >20 y	ASD (18)	Triage BNP ELISA	8	282 ± 10(SD) fmol/ml	<5.0 (<5.0-5.6) pg/ml 367 ± 56(SD) fmol/ml	< 0.001	1day 6 mos	28.3 (26.0-31.7) pg/ml 348 ± 7 (with FA) 303 ± 19 (without FA)	P = 0.012 < 0.001

ANPN = N terminal pro-atrial natriuretic peptide, AS = stenosis of the aortic valve, ASD = atrial septal defect of secundum type, ASDpr = atrial septal defect of primum type, BNP = brain/ B-type natriuretic peptide, CoA = coarctation of the aorta, CP= constrictive pericarditis, DCM = dilated cardiomyopathy, EF = endocardial fibroelastosis, ELISA = Enzyme-Linked Immunosorbent Assay, HF = heart failure, mo = month/ months, PAPVR = partial anomalous pulmonary venous return, PDA = patent ductus arteriosus, PS = stenosis of the pulmonary valve, RCMP = restrictive cardiomyopathy, RIA = radioimmunoassay, TGA = transposition of great arteries, TI = tricuspid insufficiency, Trunc = truncus arteriosus with conduit stenosis, VSD = ventricular septal defect, y = year/ years

Triage BNP Biosite, San Diego, California

Shionogi RIA, Shionogi, Osaka, Japan

Elecsys system = An electrochemiluminescence immunoassay; Roche diagnostic Corporation, Mannheim, Germany

Biomedica = A competitive Enzyme Immunoassay; Biomedica, Vienna, Austri

4.3. Congenital heart defects

4.3.1. Volume overload

4.3.1.1. Atrial septal defect

Mean incidence of ASD is 941 per million live births (Hoffman and Kaplan 2002), with a 2:1 female predominance (Veldtman et al. 2004). The natural history of ASD during childhood involves little disability. After the third decade, life-expectancy drops, and morbidity and mortality rise (Campbell 1970b).

The physiological sequelae of ASD depend on the size of the defect, the relation of the diastolic compliance of RV and LV, and the ratio of pulmonary to systemic vascular resistance (Borow and Karp 1990). Possible consequences of ASD in addition to volume overload of the right atrium and ventricle are pulmonary artery hypertension, increased pulmonary vascular resistance, insufficiency of right-sided valves, and atrial arrhythmias (Dexter 1956, Borow and Karp 1990). Even though PH has usually developed after the third decade, there are studies do show infants, young children, and adolescents with ASD having PH (Wagenvoort et al. 1961, Craig and Selzer 1968, Cherian et al. 1983, Haworth 1983, Steele et al. 1987).

Typical abnormal physical signs with ASD are a hyperactive RV impulse, widely split fixed second-heart sound, systolic murmur, and early- to mid-diastolic flow murmur at the left sternal border. The ECG abnormalities are right-axis deviation, evidence of right atrial enlargement, and RV conduction delays (Davignon et al. 1980, Christensen et al. 2005). In chest X-rays, the cardiothoracic ratio is greater than 0.5, and pulmonary vascular markings are increased (Porter et al. 2001). Concern about the possibility of patients' having a hemodynamically significant ASD without classical signs have arisen from a study with 7% of its study population's lacking any typical physical or ECG findings (Christensen et al. 2005). However, spontaneous ASD closure did occur despite signs of heart failure during infancy (Brassard et al. 1999, Helgason and Jonsdottir 1999). Controversy exists about the possibility of a significant increase in diameter of the defect (McMahon et al. 2002).

Variations in size, position, shape, and rims of the defect are widespread and have an influence on closure method. The first successful surgical repair of the ASD was described more than 50 years

ago (Gibbon 1954). The first percutaneous ASD closure in humans was described over 30 years ago (King et al. 1976, Mills and King 1976).

Surgical repair has had good results, with a low incidence of residual shunts and low mortality from earlier decades of surgery. Complications include transient arrhythmias, respiratory tract infections, pericardial effusion or pneumothorax, anemia, heart failure, transient atrioventricular block, severe bleeding, reoperation, and thrombus formation (Butera et al. 2006). After surgical correction, patients with dilatation of the right side of the heart are at risk for rhythm disturbances (Pearlman et al. 1978, Attenhofer Jost et al. 2002). Complete abolition of shunts has been achieved in 93% of patients, and mortality rate has decreased from 3.4% (Cohn et al. 1967) to close to zero (Richenbacher et al. 1989). Predictors of postoperative symptoms and of long-term survival are age at operation and systolic pressure in the main pulmonary artery before operation (Murphy et al. 1990, Groundstroem et al. 1999).

Percutaneous closure of ASD has low complication rates ranging from zero (Masura et al. 2005) to 8.6% (Pedra et al. 2000, Chessa et al. 2002). Complications include ST segment elevation, secondary bleeding with groin hematoma, and vein injury (Chessa et al. 2002), retroperitoneal bleeding and air embolism (Fischer et al. 2003), and device malposition (Rocchini 1990). Thrombus formation on the device has an overall incidence of 1.2%. Risk factors for thromboembolic complications are an atrial septal aneurysm and atrial fibrillation (Chessa et al. 2002, Krumdorf et al. 2004). Device embolization occurs in 0.55% (Levi and Moore 2004). Erosions of the atrial wall or of the aortic root have been reported with an incidence of 0.1% (Chun et al. 2003, Trepels et al. 2003, Preventza et al. 2004, Knirsch et al. 2005).

Long-term outcome after surgical repair of ASD in childhood is comparable with longevity of healthy controls. Actuarial 27-year survival rate in patients operated on at ages younger than 24 years is 97% and that of controls 93%. If operated on later, after the third decade, life expectancy is reduced as compared with controls (Murphy et al. 1990), and patients have more symptoms (Groundstroem et al. 1999).

In catheterization, reduced stroke volume has been evident in patients (children and adults) with ASD as compared with control values (Levin et al. 1975, Popio et al. 1975). Altered diastolic LV function with increased muscle stiffness and reduced compliance of LV has occurred before closure (Booth et al. 1988). Shunting through the ASD causes underfilling of the LV, and at the same time

the volume overload of the RV disturbs septal motion (Dexter 1956, Popio et al. 1975, Bonow et al. 1981). Study of LV function during the pressure and volume overload of the RV has shown the influence of septal motion on FS and the EF of the LV (Louie et al. 1995). In volume overload of the RV, the septal motion towards the cavity of the LV happens during the end diastole and causes a decrease in the EF of the LV (Louie et al. 1995, Walker et al. 2004). The diastolic and systolic function of the LV can thus be mechanically disturbed, with changes apparently reversible (Bonow et al. 1981).

Acute improvement in preload and early diastolic function of the LV after percutaneous ASD closure in children depends on the preclosure magnitude of the RV volume overload and is associated with disappearance of abnormal ventricular septal motion and achievement of a more advantageous ventricular interdependence (Giardini et al. 2005). After ASD repair, end-diastolic interventricular septal flattening decreases, and at the same time LV symmetry and LV EF increase. LV symmetry increases months after surgical ASD repair (Mathew et al. 1976, Hart et al. 2004, Walker et al. 2004).

In one study comparing percutaneous to surgical closure, acute decrease in RV volume after ASD closure between groups was similar (Berger et al. 1999). In children after surgical repair, an initial decrease occurred during the first 3 months, but dilatation was evident in over 80% up to 5 years after this procedure (Meyer et al. 1982). End-diastolic diameter of the RV decreases after closure of the defect, but diameter remains enlarged as compared with controls' values, in some cases even when it was percutaneously closed (Pearlman et al. 1978, Pedra et al. 2000, Shaheen et al. 2000, Du et al. 2001, Veldtman et al. 2001, Muta et al. 2002, Salehian et al. 2005). RV and LV end-diastolic volumes as measured by MRI were, however, comparable between patients with ASD surgically repaired in childhood and controls (Bolz et al. 2005). After device closure, the end-diastolic diameter of the RV decreased and that of the LV increased further more and diastolic function improved (Pawelec-Wojtalik et al. 2006).

Based on the myocardial performance index and tissue Doppler imaging, preservation of LV function is possible after both the percutaneous (device) and the surgical ASD closure, but the RV function was preserved only after the device closure (Dhillon et al. 2002, Cheung et al. 2004, Abd El Rahman et al. 2005). Not all findings have been in accordance with this. Even LV function in addition to RV function can be impaired after either closing method (Di Salvo et al. 2005). On the

other hand, based on myocardial performance index has shown, after percutaneous closure, improvement of both RV and LV function (Salehian et al. 2005).

After closure of the defect, end-diastolic diameter and volumes of LV and RV change towards normal values (Nakazawa et al. 1977, Wanderman et al. 1978, Salehian et al. 2005). After the surgical correction, no differences are evident in transmitral Doppler flow recordings between patients (both children and adults) and controls (Simmers et al. 1994).

In adult patients, postoperative plasma levels of brain natriuretic peptide were higher in those undergoing the surgical repair than in controls, with a correlation noticed with age at follow-up, age at repair, presence of diastolic dysfunction, and with the left atrial size. No correlation was evident with the dilatation of the RV (Attenhofer Jost et al. 2002). In adults with ASD, plasma ANP levels correlated with degree of the pulmonary blood flow, and levels of BNP correlated with magnitude of the mean pulmonary artery pressure (Nagaya et al. 1998). After percutaneous ASD closure, elevated levels of cardiac troponin I have been measured; the reason may be release of the cytosolic pool of cardiac troponins due to the reversible membrane instability of myocardial cells after device placement (Pees et al. 2003).

4.3.1.2. Patent ductus arteriosus (PDA)

The ductus arteriosus is a channel between the pulmonary trunk and the descending aorta that is widely patent in the fetus, but after birth is constricted, with permanent closure within the first week of life (Rudolph 2001a).

Incidence of the patent ductus arteriosus (PDA) is estimated at approximately 799 per million live births (Hoffman and Kaplan 2002), with 2.3 times as high in girls as in boys (Campbell 1968).

PDA causes volume overload of the left side of the heart (Samanek 1992). Complications include heart failure, infective endarteritis, PH, aneurysm of the duct, and thromboembolism. Congestive heart failure may develop either in infancy or during adult life (Campbell 1968).

Clinical manifestations of PDA are presence of a cardiac murmur, increased precordial cardiac pulsatility, and bounding pulse due to increased pulse pressure (Rudolph 2001a). ECG findings are usually normal with small shunts, but with larger shunts may result in LV hypertrophy and LA

enlargement may be present (Buck 2004). In chest X-rays, PDA may cause an increase in pulmonary arterial markings and increase in heart size with LV prominence (Rudolph 2001a). Gross performed the first successful ligation of the PDA (Gross and Hubbard 1939). Today, the operative mortality is less than 2%, and less than 1% when premature infants and patients with PH are excluded (Jones 1965, Panagopoulos et al. 1971, Peirone and Benson 2004). Residual shunts have been reported to occur in from zero (Prieto et al. 1998) to 23% of cases after surgery (Sorensen et al. 1991). Surgical complications include reoperation for bleeding or for inadequate ligation, chylothorax or other pleural effusion, recurrent laryngeal nerve injury, atelectasis, pneumonia, rhythm disturbances, wound infection, and pneumothorax (Mavroudis et al. 1994, Vanamo et al. 2006).

Porstmann performed in 1967 the first interventional closure of PDA (Porstmann et al. 1967). Percutaneous closure of the PDA is nowadays an effective method for most patients with PDA. Coils are used for closure of small-sized PDAs, and different duct occluders for moderate and large PDAs. Amplatzer duct occluders are safe, with high complete-closure rates (Masura et al. 1998, Bilkis et al. 2001, Pass et al. 2004, Masura et al. 2006). The reopening rate of PDA after its successful coil occlusion has ranged from zero (Patel et al. 1999) to 25% (Daniels et al. 1998). On the other hand, no reopening has been observed later with complete closure evident in echocardiography at the 6-month follow-up (Turner et al. 2002). Prevalence of residual shunts 20 months after a single coil procedure has been estimated at $6 \pm 5\%$ (Shim et al. 1996). No reopening has been reported after closure of PDA with the Amplatzer occluder (Masura et al. 2006).

Complications of percutaneous occlusion of PDA include embolization of the device to the pulmonary artery or to the descending aorta, hemolysis due to residual flow, femoral venous or arterial damage, or obstruction of the left pulmonary artery or descending aorta (Thanopoulos et al. 2000, Bilkis et al. 2001, Masura et al. 2006).

Few studies compare surgical and percutaneous PDA closure. Cost-effectiveness analyses have shown percutaneous coil occlusion to be as effective as and less costly than surgical closure if silent residual shunts were not considered clinically significant. A residual shunt was detected in 17% of 24 patients with coil occlusion, but none had a residual shunt in the echocardiography after the surgical closure. However, only 42% of patients with the surgical closure had echocardiography analysis done afterwards. Those with percutaneous closure needed a shorter hospital stay (Prieto et al. 1998).

4.3.2. Pressure overload

4.3.2.1 Coarctation of the aorta (CoA)

Classical coarctation of the aorta (CoA) is a narrowing located most commonly in the region immediately distal to the origin of the left subclavian artery and opposite the ductus arteriosus diverticulum (Rothman 1998). Of congenital heart defects, CoA comprises 5 to 10%. Its incidence is 409 per million live births (Hoffman and Kaplan 2002). Most cases occur sporadically and the male to female ratio range from 1.27:1 to 1.74:1 (Benson and McLaughlin 2004). CoA causes a pressure overload on the LV.

The clinical manifestation of CoA varies depending on severity of obstruction and the presence of associated cardiac defects. Infants may suffer progressive respiratory distress, tachycardia, and weak femoral pulses. Pulmonary rales may be audible, and hepatomegaly may be evident. In older children, clinical examinations may reveal weak femoral pulses, a pressure gradient between arm and leg, and arterial hypertension (Rudolph 2001b). Diagnosis can usually be made accurately with 2D echocardiography and with Doppler tracings of blood flow velocities. In older children and adults, MRI or CT and sometimes cardiac catheterization with angiography may be necessary for diagnostics and for decision-making regarding treatment (Rothman 1998). MRI or CT is necessary for detection of aneurysms after surgical and catheter intervention.

In ECG, right axis deviation and RV hypertrophy is present in infants under 3 months old. In children, ECG may reveal an increase in LV forces, and RV conduction delays. In older children and in adults, ST depression and T-wave flattening or inversion in leads I, V5, and V6 may occur (Rudolph 2001b). In chest X-rays in children, heart size is normal or moderately enlarged with LV prominence. An indentation may be seen along the left margin of the aortic shadow just beyond the aortic arch (Rudolph 2001b).

Cardiac malformations associated with CoA include bicuspid aortic valve in up to 85% (Ward 2000, Warnes 2003), mitral valve abnormalities, and ventricular septal defects (Koller et al. 1987, Rothman 1998). Incidence of subacute bacterial endocarditis has been between 0.6 to 1.3% per annum (Campbell 1970a).

The following indications for intervention are used in various centers: peak-to-peak pressure gradient in catheterization of 25 to 30 mm Hg (Beekman et al. 1987, Mendelsohn et al. 1994); a systolic blood pressure over the 95th percentile for age and uncontrolled hypertension with congestive heart failure (Rao et al. 1988), or a discrete CoA, upper extremity hypertension, and resting arm-to-leg gradient of 20 mm Hg or more (Mendelsohn 1995). In the presence of large collaterals, a large PDA, or severe LV dysfunction, the pressure gradient may be less than assumed from the degree of obstruction (Glancy et al. 1983, Rothman 1998). Prior to CoA repair, hypertension is a common manifestation, causes a pressure load on the LV, and can cause myocardial hypertrophy and diastolic and systolic dysfunction (Rothman 1998). Upper body hypertension may be caused by mechanical obstruction, diminished distensibility of the aorta and its branches proximal to the CoA (Gardiner et al. 1994, Guenthard and Wyler 1995), or resetting of aortic baroreceptors (Sehested et al. 1982, Beekman et al. 1983).

Surgical repair with resection and end-to-end anastomosis was first described by Crafoord and Nylin in 1945 (Crafoord and Nylin 1945). The other techniques include patch aortoplasty, left subclavian patch aortoplasty, and bypass grafts between the ascending and descending aorta (Rothman 1998). Operative mortality has varied according to age at operation. Acute mortality ranges from 3 to 32% if all operated patients with CoA are taken into account (Craig and Selzer 1968, Koller et al. 1987, Cohen et al. 1989, Knott-Craig et al. 1993, Kappetein et al. 1994, Merrill et al. 1994, Backer et al. 1995), and in isolated CoA, the mortality range has been from zero to 2% (Merrill et al. 1994, Conte et al. 1995). Complications after surgical repair of CoA include hemorrhage, unilateral vocal cord paralysis, phrenic-nerve damage with ipsilateral diaphragmatic paralysis, chylothorax, residual or recurrence of CoA aneurysm of the aorta, myocardial infarction, and bacterial endocarditis (Koller et al. 1987, Rothman 1998). Aneurysm formation has been detectable no matter which technique has been used (Martin et al. 1988, Ala-Kulju and Heikkinen 1989, Aebert et al. 1993, Fujita et al. 1996).

Rate of recurrence of CoA (reCoA) varies inversely with age at surgical repair: in neonates, up to 50% (Brouwer et al. 1994, Backer et al. 1995, Pfammatter et al. 1996), in infants 26%, 15% at age 6 months (Brouwer et al. 1994), and 3% for all patients (Cohen et al. 1989).

Percutaneous dilatation for reCoA was described in 1982 (Singer et al. 1982) and for native CoA in 1983 (Lababidi 1983). Balloon angioplasty produces a controlled injury of the intima and part of the media, increasing vessel diameter, and healing by means of a fibrous scar over a period of months

(Lock et al. 1982, Suarez de Lezo et al. 1984). Success rate is from 78 to 91% (Mendelsohn et al. 1994, Fletcher et al. 1995). During follow-up, improvement in the diameter and contour of the CoA segment has been described as studied by control catheterization and angiograms (Suarez de Lezo et al. 1984, Beekman et al. 1987, Rao and Carey 1989) or by MRI (Weber et al. 1996).

Balloon angioplasty in neonates and infants is controversial, but there are small studies with good acute results (Lababidi 1992, Mendelsohn et al. 1994, Fletcher et al. 1995, McCrindle et al. 1996, Rao et al. 1996). In one study, recurrence rate was higher in the neonate subgroup (83%) and in the infant subgroup (39%) than in children (8%) after balloon dilatation of native CoA, overall incidence of reCoA being 25%. Aneurysm formation was noticed in 5% of patients, and 23% of children had blood pressure above the 95th percentile value (Rao et al. 1996). In another study on neonates and infants with intractable heart failure treated with balloon dilatation, the actuarial survival probability was 83% at 19 years, with 23% needing no reintervention (Suarez de Lezo et al. 2005). Due to the high incidence of reCoA, balloon dilatation is generally not recommended treatment for native CoA in patients under 6 to 12 months of age. The immediate success rate after balloon dilatation for reCoA has ranged from 65 to 100% (Saul et al. 1987, Cooper et al. 1989, Hijazi et al. 1991, Anjos et al. 1992, Witsenburg et al. 1993, McCrindle et al. 1996, Yetman et al. 1997, Maheshwari et al. 2000). Rate of restenosis has ranged from 16 (Maheshwari et al. 2000) to 30% (Anjos et al. 1992).

Mortality rate has ranged from zero (Fletcher et al. 1995, Mendelsohn 1995, Rao et al. 1996) to 7% (Rao and Chopra 1991), and other major complications in percutaneous dilatations of CoA and reCoA include cerebrovascular accident and aortic tear. Aneurysm formation has been reported in 2 to 6% of patients (Hijazi et al. 1991, Anjos et al. 1992, Witsenburg et al. 1993, Yetman et al. 1997) and up to 43% in native CoA (Cooper et al. 1987, Saul et al. 1987, Cooper et al. 1989, Tynan et al. 1990, Lababidi 1992). An aneurysm has been evident after percutaneous dilatation of reCoA in 2% to 6% (Rocchini and Beekman 1986, Mendelsohn et al. 1994, Fletcher et al. 1995, Rao et al. 1996).

Despite early and apparently successful repair of CoA, morbidity is increased. Myocardial hypertrophy may persist despite LV remodeling taking place after successful CoA repair (Moskowitz et al. 1990, Krogmann et al. 1993, Johnson et al. 1994, Kimball et al. 1994, Sigurdardottir and Helgason 1997, Pacileo et al. 2001). LV function can be hyperdynamic after CoA repair (Moskowitz et al. 1990, Kimball et al. 1994, Pacileo et al. 2001), and the prevalence of systemic hypertension after CoA repair is higher with longer follow-up: after 8 years 13% (Katz et

al. 1987) and after 30 years as high as 68% (Presbitero et al. 1987). The probability for late hypertension has been more than 10% even if surgery occurs during neonatal life (Brouwer et al. 1994), and up to 24% of those operated on during infancy have elevated resting blood pressure (Koller et al. 1987, Cohen et al. 1989, Pfammatter et al. 1996). Despite normal blood pressure at rest, values may be abnormally high during ambulatory measurement or during a stress test, and LV mass has been increased in echocardiography (Koller et al. 1987, Leandro et al. 1992, Hauser et al. 2000). Postoperative hypertension is associated with this morbidity and mortality (Koller et al. 1987). Vascular “programming” may happen very early, and altered baroreflex function may have an influence on evolving postoperative hypertension (Beekman et al. 1983, de Divitiis et al. 2001). The intima-media thickness of the carotid and femoral arteries has been higher in patients with CoA, irrespective of the fact that previous repair has been successful and their ambulatory blood pressure is normal. Age at repair is an independent predictor of femoral intima-media thickness but not of carotid intima-media thickness (Vriend et al. 2006). Despite successful CoA repair, paradoxical hypertension develops in up to 18% (Wright et al. 2005).

Due to increased co-morbidity after repair of CoA, estimated survival remains reduced, being 92% after 30 years (Presbitero et al. 1987) and 73% to 80% some 40 to 50 years after surgery (Cohen et al. 1989, Brouwer et al. 1994). However, survival for patients operated on when younger than age 10 is as high as 97% (Brouwer et al. 1994). Late death may be due to cardiovascular complications: coronary artery disease (Meyer et al. 2005), circulus Willis aneurysm, or cerebrovascular accidents (Cohen et al. 1989).

4.4.3. Pericardial constriction and myocardial restriction

Mulibrey nanism

Mulibrey nanism is an autosomal recessive disease caused by mutations in the TRIM37 gene on chromosome 17q22-q23 (Avela et al. 2000). This gene encodes the peroxisomal TRIM37 protein of unknown function (Avela et al. 1997, Karlberg et al. 2004). Five different mutations have been reported in patients with the MUL gene. Two of these occur mostly in the Finnish population: the Finn major and Finn minor mutations (Karlberg et al. 2004) causing severe, prenatal-onset growth failure and multiple organ manifestations (Perheentupa et al. 1973, 1975, Karlberg et al. 2004). Quality of life and life-expectancy are influenced by heart manifestations. Mulibrey heart disease includes constrictive pericarditis (Perheentupa et al. 1973, Tuuteri et al. 1974) and myocardial hypertrophy with a variable degree of myocardial fibrosis in any combination (Lipsanen-Nyman et

al. 2003). One study involved 49 patients with the Finnish type of Mulibrey nanism. During the follow-up, up to 25 years, 25 had developed congestive heart failure; 19 had undergone pericardiectomy for constrictive pericarditis, 12 with long-term clinical benefit (Lipsanen-Nyman et al. 2003).

Constrictive pericarditis

Constrictive pericarditis (CP) is an uncommon disorder with multiple causes, e.g., idiopathic, infectious, radiation, chest trauma, cardiovascular surgery, heart transplantation, connective tissue diseases, neoplasm, and Mulibrey nanism (Myers and Spodick 1999, Wood and Picard 2004). In one report, among 75 adult patients, constrictive pericarditis was idiopathic in 46% and postsurgical in 37%, and was due to mediastinal irradiation in 9% (Bertog et al. 2004). The pericardium is thickened, fibrotic, and frequently calcified, leading to decreased compliance, impaired diastolic cardiac function and finally heart failure (Myers and Spodick 1999, Bertog et al. 2004).

Constrictive pericarditis often has an insidious onset with symptoms of systemic and pulmonary venous congestion. The jugular venous pulse may be elevated, and an abnormal third heart sound heard. On the other hand, pulsus paradoxus, a reduction in arterial pressure of more than 10 mm Hg during inspiration, is not a typical sign (Myers and Spodick 1999). ECG may reveal widespread ST-segment flattening with a low, flat, or inverted T wave. QRS voltages may be diffusely low, sometimes with right axis deviation (Myers and Spodick 1999).

Normally, the inspiratory decrease in intrathoracic pressure is transmitted to all cardiac chambers as well as to the pulmonary veins. In constriction, the encasing pericardium isolates the cardiac chambers from changes in intrathoracic pressure. The pressure gradient between pulmonary veins and LV decreases with inspiration. This causes a reduction in the velocity of diastolic flow in the pulmonary veins and a reduction in left-sided filling. With this is associated an increase in RV diastolic filling, and the interventricular septum moves towards the LV. Expiration has the opposite effect: Flow into LV increases, and the septum shifts rightward; in addition a reduction occurs in transtricuspidal flow velocity (Myers and Spodick 1999). Cardiac output is dependent on heart rate. By Doppler echocardiography, a typical observation in transmitral flow is that E and A velocities decrease during inspiration over 25% with no significant change in E/A ratio (Myers and Spodick 1999).

MRI and CT enable accurate measurements of pericardial thickness but not of elasticity. Radionuclide ventriculography has shown that patients with constrictive pericarditis have shorter time to peak filling rate (TPRF) than do controls or patients with restrictive cardiomyopathy (Aroney et al. 1989, Myers and Spodick 1999). PFR is higher in CP than in restrictive cardiomyopathy (RCM) or in controls (Aroney et al. 1989). In another study, PFR was higher in patients with CP than in controls, but after pericardiectomy no difference was evident (Gerson et al. 1989).

Restrictive cardiomyopathy

RCM accounts for 2 to 5% of cases with pediatric cardiomyopathies. Only a few reports concern pediatric patients with RCM (Mehta et al. 1984, Gewillig et al. 1996, Denfield et al. 1997). Clinical signs and symptoms of RCM result from increased stiffness of the myocardium. Both myocardial and endomyocardial types of RCM exist. Myocardial RCM has subtypes called noninfiltrative (idiopathic, familial, hypertrophic, diabetic cardiomyopathy), infiltrative (amyloidosis, sarcoidosis), and storage disease (Fabry's disease). Endomyocardial RCM has subtypes involving carcinoid heart disease, radiation, and toxic effects of anthracycline (Kushwaha et al. 1997). In children, RCM is usually idiopathic or associated with cardiac hypertrophy and fibrosis.

Symptoms are similar to those seen in CP: dyspnea, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, general fatigue, and weakness. Clinical signs include rise in jugular venous pulse, peripheral edema, ascites, enlarged and pulsatile liver, third heart sound, sinus tachycardia, and low pulse volume (Kushwaha et al. 1997). Pulmonary hypertension, high pulmonary vascular resistance, and embolic complications cause morbidity in RCM in childhood (Denfield et al. 1997). In ECG, signs are of LA dilatation and repolarization abnormalities.

Children with RCM have a poor prognosis without transplantation (Denfield et al. 1997, Kushwaha et al. 1997, Russo and Webber 2005). In one study, end-diastolic pressures of the RV and LV and the ratio LA/Ao at presentation had a significantly negative correlation with survival time after diagnosis. Conversely, no association occurs with age at presentation, sex, or presence or absence of heart failure symptoms at presentation (Russo and Webber 2005). In addition, increased risk for sudden death (without congestive heart failure) has been associated with female gender-with chest pain or syncope or both at presentation. Evidence for ischemia from the Holter monitor predicted death within months in a study comprising children, mostly under age 6 (Rivenes et al. 2000).

In echocardiography, RCM is characterized by diastolic dysfunction: impaired diastolic filling with normal or decreased diastolic volume of either or both ventricles (Denfield et al. 1997, Kushwaha et al. 1997, Tam et al. 2002). Biventricular systolic function is usually normal or only mildly abnormal. Biatrial dilatation is often present, with either the absence or presence of ventricular hypertrophy or dilatation (Mehta et al. 1984, Gewillig et al. 1996, Kushwaha et al. 1997, Russo and Webber 2005). Doppler echocardiography shows the typical transmitral flow pattern of increased E wave (≥ 1.0 m/s) and decreased A wave (≤ 0.5 m/s), increased E/A ratio (≥ 1.5 -2) with no respiratory variation, and decreased DT (≤ 150 ms) (Gewillig et al. 1996, Kushwaha et al. 1997, Tam et al. 2002). In addition, mitral or tricuspid valve regurgitation is common (Kushwaha et al. 1997).

In childhood, progression of RCM can vary significantly from a slow disease process to an aggressively progressing disease with cardiac failure and a need for heart transplantation (Gewillig et al. 1996, Denfield et al. 1997).

Differentiation of constrictive pericarditis from restrictive cardiomyopathy is essential, as in the latter no curative treatment exists, but in CP, pericardiectomy can lead to relief of symptoms (Troughton et al. 2004).

Plasma levels of brain natriuretic peptide are higher in patients with RCM than in those with CP (Leya et al. 2005). In adult patients with impaired diastolic LV function, mean BNP concentrations have been higher than in those with normal diastolic LV function (Lubien et al. 2002).

5. AIMS OF THE STUDY

The specific aims in detail were to evaluate prospectively:

1. the influence of right ventricular volume overload caused by atrial septum defect (ASD) on cardiac function in children before and after surgical and percutaneous ASD closure
2. the influence of percutaneous treatment on size and function of the left ventricle (LV) in patients with volume overload of LV caused by patent ductus arteriosus (PDA)
3. the influence of pressure overload on LV in children undergoing percutaneous or surgical repair of coarctation of the aorta (CoA)
4. and to evaluate cardiac function in children with Mulibrey nanism by utilizing 2D and 3D echocardiography
5. the usefulness of 2D and 3D echocardiography and measurement of serum levels of natriuretic peptides for hemodynamic evaluation in children with various types of congenital heart defects.

6. PATIENTS AND METHODS

6.1. Patients

The study was carried out at the Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland, between February 2003 and February 2006. All the parents of the participants agreed to participate in this clinical trial approved by the hospital ethics committee and gave their written informed consent.

The demographics of patients and controls are presented in Table 4. All patients and controls underwent a clinical cardiovascular examination and blood-test sampling for measurement of natriuretic peptides at the time of the echocardiographic examinations. Control children were examined once by 2D and 3D echocardiography. Patients were examined prior to the intervention and twice or three times thereafter according to the normal protocol. The control children were asymptomatic with no abnormalities in clinical examination, ECG, or echocardiography.

6.1.1. Right ventricular volume overload in patients with ASD (Study I)

Hemodynamically significant ASD was diagnosed in our unit in 41 pediatric patients aged more than 2 years between February 2003 and May 2005. Based on transthoracic or transesophageal echocardiography, 17 children were considered suitable and 24 unsuitable for percutaneous closure. The study group consisted of the 17 patients scheduled for catheterization and 7 patients scheduled for surgical ASD closure. The control group comprised 51 healthy children.

All patients with ASD were asymptomatic. The children with ASD were examined by transthoracic 2D and 3D echocardiography prior to ASD closure and one, 6 and 12 months thereafter. The children treated with percutaneous ASD closure underwent transesophageal echocardiography (TEE) and standard hemodynamic cardiac catheterization prior to the procedure.

Table 4. Characteristics of subjects in the study groups as median (range)

Group	N	Gender (m/f)	Age (years)	Weight (kg)	Height (cm)	BSA (m ²)	HR at baseline	P value as compared with controls' HR
ASD pts	24	3/21	6.9 (2.3-18.5)	22.0 (12.4-64.7)	117.1 (83.0-163.0)	0.84 (0.53-1.68)	95 (63-127)	0.197
Control	51	20/31	6.9 (2.5-15.6)	23.6 (9.8-62.5)	119.0 (75.0-173.0)	0.87 (0.43-1.75)	89 (55-119)	
PDA pts	33	13/20	2.6 (0.9-10.6)	13.0 (6.9-32.8)	88.0 (70.0-140.5)	0.5 (0.4-1.1)	107 (72-174)	0.330
Controls	36	13/23	3.3 (0.2-10.7)	15.3 (5.4-39.2)	97.8 (56.5-146.8)	0.6 (0.3-1.3)	102 (67-155)	
CoA pts	28	18/10	3.50 (0.01-19.02)	16.65 (3.36-73.00)	100.1 (48.0-171.0)	0.67 (0.20-1.84)	97 (44-214)	0.787
CoA with follow-up	15	6/9	2.00 (0.01-14.65)	14.00 (3.36-56.60)	91.5 (49.5-164.0)	0.59 (0.20-1.57)		
Controls	28	18/10	4.19 (0.07-14.12)	16.25 (3.46-62.50)	102.1 (53.0-163.5)	0.67 (0.22-1.64)	101 (55-169)	
Mulibrey nanism pts	26	12/14	6.8 (0.4-15.9)	13.4 (3.9-35.0)	97.5 (54.3-140.4)	0.60 (0.23-1.15)	92 (58-143)	0.064
Control	26	12/14	6.8 (0.3-15.6)	23.3 (6.5-62.5)	120.7 (62.0-173.0)	0.88 (0.32-1.75)	84 (55-139)	

ASD = atrial septal defect; BSA = body surface area, CoA = coarctation of the aorta; f = female, HR = heart rate; m = male; N = number; PDA = patent ductus arteriosus

6.1.2. Left ventricular volume overload in patients with PDA (II)

Between February 2003 and March 2004, 38 pediatric patients aged more than 6 months were diagnosed with PDA. The indication for PDA closure in our institution is either systolic or continuous murmur (Allen et al. 1998). Based on transthoracic echocardiography, one child was considered unsuitable for the percutaneous closure. The control group comprised 36 healthy children matched for age, sex, height, weight and BSA.

The 37 children with PDA were taken to the cardiac catheterization laboratory for percutaneous occlusion of the PDA. They underwent 2D and 3D echocardiography examinations prior to the catheterization and standard hemodynamic cardiac catheterization and angiography of the distal aortic arch. Three patients unsuitable for catheter closure of the PDA and one with a mild aortic stenosis were excluded. The study group comprised the remaining 33. In this group, one child had clinical signs of congestive heart failure and was treated with diuretics prior to PDA closure, but all others were asymptomatic. One child was diagnosed with Mulibrey nanism.

6.1.3. Left ventricular pressure overload in patients with CoA (III)

In our unit, 34 pediatric patients were diagnosed between June, 2003, and November, 2004 with unoperated (native) CoA or recurrent coarctation of the aorta (reCoA) requiring intervention. The indication for intervention in a CoA is an arm-leg systolic gradient of 20 mm Hg or more (Mendelsohn 1995). Of these 34 children, 23 had native CoA, and 11 had reCoA. Of these 11, 10 had undergone surgery and one balloon angioplasty for CoA. Three babies with critical CoA, a patient with surgically treated Taussig-Bing anomaly, one with mild mitral valve prolapse and regurgitation, and one with surgically treated ventricular septal defect and aortic stenosis were excluded. The patient group then comprised the remaining 28 children. The control group comprised 28 healthy voluntary children matched for age, sex, height, weight, and BSA.

Of 34 children diagnosed with CoA, 20 underwent standard hemodynamic cardiac catheterization and angiography of the aortic arch: 11 of them had native CoA, and 9 had reCoA. Percutaneous balloon angioplasty was performed in 11 patients, 2 of these with stent implantation. The patients aged less than 6 months with native CoA and those judged by invasive or uninvaseive methods to be unsuitable for percutaneous treatment were referred for surgical repair. A total of 17 patients

underwent surgical repair either with resection or with extended resection of the CoA segment plus end-to-end anastomosis, or with angioplasty with a patch or tube prosthesis.

Of the same 34, 15 patients had a bicuspid aortic valve. In one of them, it was moderately stenotic, and became severely stenotic one month after operation for the CoA and he was booked for catheterization and valvuloplasty and excluded from further analysis. One patient had severe LV dysfunction and heart failure, and one was diagnosed with Turner's syndrome. One patient with reCoA had been successfully operated on for ventricular septal defect several years earlier. Two patients were on medication for hypertension, 11 complained about headache or decreased exercise tolerance, and 17 were asymptomatic.

6.1.4. Cardiac dysfunction in children with Mulibrey nanism (IV)

In Finland, a total of 30 children aged less than 16 years have been diagnosed with Mulibrey nanism. Of these patients, 26 (87%) participated in this study. They were examined between April 2003 and April 2005. During this study period, 10 patients were examined twice to discover any changes in myocardial function during the follow-up of 6 to 12 months. The control group comprised of 26 healthy children matched for age and gender.

6.2. Methods

6.2.1. Clinical examinations

A normal clinical examination was performed. Weight and height of all subjects were recorded and body surface area (BSA) was calculated (DuBois and DuBois 1916). Blood pressure was measured oscillometrically (Dinamap) from the right arm with the cuff covering two-thirds of the upper arm. The systolic arm-leg blood pressure gradient was measured as the positive difference between systolic blood pressure of the right arm and of the right or left leg.

6.2.2. Chest x-rays

Chest radiographs of all patients were obtained at baseline and at the follow-up visits. The cardiothoracic ratio was measured by relating the largest transverse diameter of the heart to the widest internal diameter of the chest. The pulmonary vasculature was evaluated and the correct position of occluding device and stent confirmed.

6.2.3. Echocardiography

6.2.3.1. Two-dimensional echocardiography

The echocardiographic examination took place with the patient in the supine position or in left lateral semirecumbency. All studies were carried out by one or two observers (A.E. and E.J.) at baseline and at follow-up using the Acuson Sequoia C256 echocardiography system (Siemens, Mountain View, CA, USA). Data were saved on magneto-optic disks for later analysis. An ECG tracing was recorded simultaneously with the echocardiogram. Transducer frequency was 7 MHz or 5 MHz, either or both for each patient, to provide optimal 2D imaging and Doppler echocardiographic recordings. Standard parasternal, apical, and subcostal views were used to detect cardiac abnormalities in the patients and to confirm normal cardiac anatomy among controls.

6.2.3.2. M-mode echocardiography

M-mode echocardiography was performed from the parasternal long axis view directed by 2D echocardiography (Sahn et al. 1978). The left atrium (LA)/aorta (Ao) ratio was calculated as an index of LA size. The end-diastolic and end-systolic dimensions of LV as well as the end-diastolic thicknesses of the interventricular septum and LV posterior wall were measured. LV volumes, and FS and EF as indices of contractility were then calculated, and the z scores of LV dimensions determined (Kampmann et al. 2000). FS was calculated as the ratio of the difference between the end-diastolic and systolic diameter of LV to the end-diastolic diameter of LV: $FS = (LVEDD - LVESD / LVEDD) \times 100\%$. The mean of measurements from 3 cardiac cycles for each participant was saved for analysis.

6.2.3.3. Doppler echocardiography

Left ventricular diastolic function was estimated from the mitral inflow signal obtained by Doppler echocardiography. Transmitral flow velocity patterns were recorded from the apical 4-chamber view, with the sample volume being positioned between the tips of the mitral valve leaflets. We measured early peak flow velocity (E) and atrial peak flow velocity (A) and calculated the E/A ratio. The early and atrial time velocity and the total flow time velocity integrals (Evti, Avti, EAvti) were measured and the velocity time integral ratio (Evti/EAvti) calculated. In addition, we measured the deceleration time (DT) of the E velocity and deceleration rate of the early diastolic flow.

6.2.3.4. Three- dimensional echocardiography

All 3D echocardiographies and their analysis were performed by the author. Three-dimensional echocardiography was performed with TomTec computer software system (TomTec Imaging Systems GmbH, Munich, Germany). A series of cross-sectional echocardiographic images was obtained from the apical view by rotating freehand scanning. Image acquisition was triggered by ECG. In freehand scanning, a sensing device determined and registered the position and orientation of the transducer during the acquisition process. A complete cardiac cycle of images was taken on a selected image plane. Images of 9 planes were collected by rotating the transducer at apical position by hand in a 180° semicircle. Scanning of the plane took place if the heart rate was within ± 20 beats/min of the average. Digitized images were saved in computer memory during acquisition. After this, the 3D dataset underwent a postprocessing procedure.

The 3D datasets were analyzed with a detached computer. After first apex and mitral valve annulus was identified on each image plane, semi-automatic border detection was performed. Manual tracing of the endocardium was then performed on the white side of the black-white boundary. Papillary muscles, if discontinuous with the myocardium, were included in the ventricular volume. End-diastolic volume was calculated from the frame at the beginning of the R wave on the ECG or from the last frame with the mitral valve still open. End-systolic volume was calculated from the frame with the smallest cavity size when the mitral valve was still closed. Time-volume curves obtained were used to determine end-diastolic and end-systolic volumes, stroke volume, and ejection fraction. With the first derivatives calculated from these curves, we measured PFR and TPFR as indices of diastolic function, and EF and PER as indices of systolic function.

In Study I, mean time-volume curves of LV were calculated to provide a visually informative representation of the volume changes in the subjects. For each subject we first calculated the time intervals from R-wave to minimum volume and from minimum volume to the end of the heart cycle. Both time intervals were divided into 20 equal parts (5%). The respective volumes were interpolated at each time point. Data on the subjects in each group were then averaged to gain a sum curve, which represents the 5% time intervals from the R-peak in ECG and the respective volumes.

6.2.3.5. Transesophageal echocardiography

At the beginning of the percutaneous closure of ASD, transesophageal echocardiography under general anesthesia, allowed evaluation of the size, number, and position of any defect. This procedure was guided by TEE.

6.2.5. Inter- and intraobserver variability

Intraobserver variability was assessed in a randomly selected subset of 12 patients by repeating all M-mode and 3D echocardiographic measurements on a separate occasion. To test the interobserver variability, all M-mode measurements of 14 randomly selected patients were performed by a second observer (E.J.) who was blinded to the results of the initial echocardiographic examination. The values are given as variability percentage (mean difference \pm 2SD).

For LV end-diastolic and systolic diameter, and LV end-diastolic and systolic volume measurements in M-mode echocardiography, the intraobserver variability was 2.2% (0.08 ± 2.58), 5.1% (0.49 ± 3.44), 5.3% (0.54 ± 10.98), and 12.0% (1.22 ± 7.44), respectively. For the same measurements, interobserver variability was 3.1% (-0.41 ± 2.38), 3.1% (0.33 ± 1.3), 8.1% (-1.41 ± 8.02), and 6.5% (0.58 ± 2.24). For 3D diastolic and systolic LV volumes, intraobserver variability was 9.5% (-0.33 ± 6.1) and 8.8% (-0.80 ± 10.74).

6.2.6. Serum natriuretic peptides

Serum samples were frozen at -20°C. Serum concentrations of N-terminal pro-brain natriuretic peptide (proBNP) were measured by the electrochemiluminometric method. The reagent kit was manufactured by Roche (Mannheim, Germany), and the samples were analyzed at Limbach Laboratory (Heidelberg, Germany). Serum concentrations of N-terminal proatriopeptide (ANPN) were measured by immunofluorometric assay. The reagents were manufactured by Medix Biochemica (Espoo, Finland) and the instruments by Delfia Research Fluorometer (Wallac, Turku, Finland).

6.2.7. Cardiac catheterization

The cardiac catheterization was performed in the Siemens Bicor catheterization laboratory under general endotracheal anesthesia, systemic heparinization, and antimicrobial prophylaxis with intravenous cefuroxime (30 mg/kg) when the device was placed. Angiographies were done by Siemens Hicor IS-2 byplane angiography equipment and for hemodynamic measurements by the Siemens Cathcor (German).

In Study **I**, oxygen saturation data were obtained from the superior caval vein, main pulmonary artery, LA, and the LV before ASD closure. The Qp/Qs ratio was calculated. For ASD closure, the Amplatzer septal occluder (AGA Medical Corp., Golden Valley, MN, USA) was used on 15 patients and the Helex device (W.L. Gore and Associates, Flagstaff, AZA, USA) on two.

The study group of 33 children with PDA in Study **II** underwent cardiac catheterization with percutaneous closure of the PDA. In 10 children, the PDA was occluded with the Amplatzer PDA occlusion device (AGA) and in 23 children, with a detachable coil (Cook, Bloomington, IN, USA). The pressure and saturation measurements came from the LV, the aortic arch, and the main pulmonary artery before the occlusion of the PDA. Angiography was performed in the distal aortic arch before and after PDA occlusion. In addition, aortic pressure was measured after occlusion.

In Study **III**, 20 children with CoA considered suitable for percutaneous dilatation of the CoA underwent standard hemodynamic cardiac catheterization, angiography of the aortic arch, and also angioplasty of the CoA segment when appropriate. The pressure gradient across the CoA segment

was measured before and after angioplasty. A Palmaz® (Cordis Corp. Miami Lakes, FL, USA) balloon expandable stent was used for two patients.

6.2.8. Surgery

In Study **I**, surgical closure of the ASD was performed via midline sternotomy with a direct suture using a normothermic (34 -36 Celsius) cardiopulmonary bypass. In Study **III**, surgical repair of CoA was performed from a left thoracotomy with resection and end-to-end anastomosis, or with angioplasty using a tube prosthesis.

6.3. Statistical methods

Statistical analyses were performed with the Statistical Package for Social Science version 12.01 (SPSS Inc., Chicago, IL, USA). The normal distribution of the continuous variables was checked by the Kolmogorov- Smirnov test. For variables derived from echocardiograms and blood samples, median and range were calculated. The Mann-Whitney test was used for statistical analysis between groups because the number of patients was small, and distribution of parameters tested by Kolmogorov-Smirnov's goodness of fit test was not normal. The Wilcoxon Signed-Rank Test was used for analysis within groups. Correlations between the 2D and 3D echocardiographic measurements and serum concentrations of natriuretic peptides were calculated with Spearman's correlation coefficient. The level of significance chosen was at $P < 0.05$.

6.4. Ethics

This study was approved by the ethics committee of the Hospital for Children and Adolescents, University of Helsinki. All parents of patients and control children gave their written informed consent and agreed to participate in the clinical trial.

7. RESULTS

7.1. Right ventricular volume overload in patients with ASD (I)

At baseline, in transthoracic 2D echocardiography, the diameter of the ASD measured a median 12 (range 7 to 21) mm. It measured a median 11 (range 8 to 20) mm in patients treated with the percutaneous technique and 19 (range 7 to 21) mm in those treated surgically ($P = 0.02$). In patients undergoing cardiac catheterization, the ASD diameter measured a median 12 (range 6 to 23) mm by TEE and 14 (range 9 to 25) mm in balloon sizing. The Qp/Qs ratio measured a median 2.0 (range 1.3 to 3.8). The data obtained in 2D and 3D echocardiography is presented on Tables 5 and 6, and Study I, Table II.

In 2D echocardiography, of the indices of LV diastolic function, the E wave and E/A ratio were lower, and the Evti, EAvti, and DT of early mitral flow were shorter in patients with ASD than in the control group (Table 6, and I, Table II). Z score (Kampmann et al. 2000) of RV end-diastolic diameter was larger, and that of LV end-diastolic diameter smaller (I, Fig.1, and Table II) than in controls. End-systolic volumes of LV adjusted to BSA were also smaller in patients than in controls.

Similarly, in 3D echocardiography, LV end-diastolic and systolic volumes adjusted to BSA were significantly smaller than in controls. No significant differences existed between patients and controls in the indices of LV diastolic function. Of the systolic indices of LV function, PER was lower in the patient group (I, Table II).

Serum concentrations of natriuretic peptides were significantly higher in patients with ASD (Table 7 and I, Fig. 2), with ANPN measuring a median 0.43 (range 0.11 to 1.40) nmol/l in patients and 0.28 (range 0.11 to 0.55) nmol/l in controls ($P < 0.001$). Those of proBNP measured 85 (range 11 to 245) ng/l in patients and 59 (range 21 to 139) ng/l in controls ($P < 0.01$).

Table 5. Two- and three- dimensional echocardiographic findings in control subjects and in the groups of children with different diagnosis measured at baseline and at last follow-up after repair, as median (range). Measurements are compared with those of controls

Diagnosis	ASD				PDA			
	controls	baseline	P value	12 mo f-u	P value	controls	baseline	P value
N	51	24		21		36	33	
IVSED	0.00	0.25	0.116	0.50	0.155	0.25	0.25	0.347
(SD)	(-2.00-5.75)	(-1.00-4.50)		(-1.50-2.50)		(-2.00-2.75)	(-1.75-4.50)	
LVPWED	-0.25	0.00	0.163	0.00	0.040	-0.50	-0.375	0.562
(SD)	(-2.00-2.00)	(-1.50-2.00)		(-1.25-1.25)		(-2.25-1.50)	(-2.00-5.00)	
RVEDD	0.25	5.00	<0.001	2.25	<0.001	-0.25	0.25	0.129
(SD)	(-1.75-2.5)	(2.25-9.75)		(-0.25-3.50)		(-1.50-2.50)	(-1.75-2.75)	
LVEDD	-0.25	-1.50	<0.001	-0.50	0.036	-0.25	0.75	0.002
(SD)	(-1.75-1.25)	(-3.75-0.00)		(-1.75-1.25)		(-1.75-1.25)	(-1.25-3.75)	
LVEDV	63.8	45.9	<0.001	60.4	0.098	62.5	78.4	<0.001
(ml/m ²)	(45.5-85.7)	(27.6-67.1)		(43.5-92.9)		(43.9-85.7)	(44.7-117.1)	
LVESV	20.8	14.2	0.001	19.4	0.800	18.2	24.5	<0.001
(ml/m ²)	(8.3-30.6)	(7.4-33.2)		(12.5-31.8)		(9.9-30.6)	(12.3-45.0)	
LVEDV3D	59.3	50.5	<0.001	65.1	0.075	54.0	58.4	0.047
(ml/m ²)	(43.8-89.5)	(31.0-69.0)		(40.0-107.6)		(32.6-74.4)	(37.7-99.4)	
LVESV3D	29.3	25.0	<0.001	33.8	0.403	27.2	30.5	0.195
(ml/m ²)	(21.1-52.8)	(16.2-39.6)		(18.1-48.9)		(14.1-42.5)	(16.2-54.0)	

ASD = atrial septal defect, CoA = coarctation of the aorta; IVSED = z score of the end-diastolic thickness of interventricular septum, LVEDD = z score of the end-diastolic diameter of left ventricle; LVEDV = end-diastolic volume of left ventricle adjusted to body surface area; LVESV = end-systolic volume of left ventricle adjusted to body surface area; LVEDV3D = end-diastolic volume of left ventricle adjusted to body surface area measured by 3D echocardiography; LVESV3D = end-systolic volume of left ventricle adjusted to body surface area measured by 3D echocardiography, LVPWED = z score of the end-diastolic thickness of left ventricular posterior wall, mo = months, PDA = patent ductus arteriosus; RVEDD = z score of the end-diastolic diameter of right ventricle, SD = standard deviation

Table 5. Two- and three- dimensional echocardiographic findings in control subjects and in the groups of children with different diagnosis measured at baseline and at last follow-up after repair, as median (range). Measurements are compared with those of controls

Diagnosis	CoA		Mulibrey nanism					
	controls	baseline	P value	12 mo f-u	P value	controls	baseline	P value
N	28	28		13		26	26	
IVSED	0.00	1.25	<0.001	1.125	0.004	0.125	1.25	0.009
(SD)	(-1.25-1.75)	(-1.75-5.00)		(-1.00-2.75)		(-1.25-1.50)	(-1.00-2.75)	
LVPWED	-0.50	0.50	0.001	0.75	0.002	-0.375	0.25	0.025
(SD)	(-2.00-1.75)	(-2.50-2.25)		(-0.75-1.75)		(-2.00-1.75)	(-1.00-3.50)	
RVEDD	0.00	-0.5	0.190	0.50	0.197	0.25	1.50	<0.001
(SD)	(-1.75-2.00)	(-2.75-2.50)		(-2.25-1.75)		(-1.75-2.50)	(-2.75- 3.75)	
LVEDD	-0.125	0.50	0.013	1.00	0.009	0.00	0.625	0.033
(SD)	(-1.50-2.00)	(-1.50-4.25)		(-0.50-2.00)		(-1.75-1.00)	(-1.25- 2.25)	
LVEDV	63.3	67.8	0.062	72.5	0.031	63.8	72.4	0.065
(ml/m²)	(42.1-87.7)	(42.5-115.6)		(52.5-82.4)		(45.5-81.5)	(47.5-104.4)	
LVESV	19.4	18.6	0.512	18.5	0.463	21.2	27.2	0.003
(ml/m²)	(7.7-30.6)	(7.9-68.1)		(9.2-32.8)		(8.3-28.7)	(14.0-59.8)	
LVEDV3D	54.2	64.6	0.302	71.4	0.143	59.7	51.9	0.040
(ml/m²)	(35.7-89.5)	(23.5-145.3)		(24.9-121.2)		(37.6-87.6)	(33.3-73.4)	
LVESV3D	27.8	32.1	0.258	30.9	0.135	29.3	26.6	0.008
(ml/m²)	(14.1-52.8)	(11.7-93.5)		(14.9-61.3)		(21.1-46.8)	(16.2-37.2)	

ASD = atrial septal defect, CoA = coarctation of the aorta; IVSED = z score of the end-diastolic thickness of interventricular septum, LVEDD = z score of the end-diastolic diameter of left ventricle; LVEDV = end-diastolic volume of left ventricle adjusted to body surface area; LVESV = end-systolic volume of left ventricle adjusted to body surface area; LVEDV3D = end-diastolic volume of left ventricle adjusted to body surface area measured by 3D echocardiography; LVESV3D = end-systolic volume of left ventricle adjusted to body surface area measured by 3D echocardiography, LVPWED = z score of the end-diastolic thickness of left ventricular posterior wall, mo = months, PDA = patent ductus arteriosus; RVEDD = z score of the end-diastolic diameter of right ventricle, SD = standard deviation

Follow-up of all patients

In 2D echocardiography, complete ASD closure was observed in transthoracic echocardiography at the first follow-up, one month after the procedure in all patients. The differences between patients and controls in the diastolic indices of LV function evident before ASD closure had, by the time of the one-month follow-up, mostly disappeared (**I**, Table II). After cessation of shunting through the ASD and the resultant increase in LV preload, the z score of the LV end-diastolic diameter (**I**, Fig. 1B) and LV end-diastolic and systolic volumes adjusted to BSA had increased and did not differ from those of controls already at the time of the one month follow-up (**I**, Table II). The z score of the RV end-diastolic diameter decreased but remained larger than in controls even after the one-year follow-up (**I**, Fig. 1A). During follow-up, the LV fractional shortening and ejection fraction remained unchanged (**I**, Table II).

In 3D echocardiography, differences between patients and controls in LV end-diastolic and end-systolic volumes adjusted to BSA disappeared after closure (Table 5). PER increased to the control level by the one-year follow-up (Table 6, and Study **I**, Table II).

After ASD closure, serum levels of ANPN decreased gradually as compared to baseline but remained higher than in controls even at the one-year follow-up (**I**, Fig. 2A). S-ANPN measured a median 0.43 (range 0.13 to 1.00) nmol/l ($P < 0.001$ as compared with controls) at one month; 0.40 (range 0.17 to 0.71) nmol/l ($P < 0.001$) at 6 months; and 0.31 (range 0.10 to 0.70) nmol/l ($P < 0.05$) one year after closure. Serum levels of proBNP increased after closure but after one year did not differ from control values (**I**, Fig. 2B). S-proBNP measured a median 138 (range 14 to 316) ng/l ($P < 0.001$) at one month; 96 (range 17 to 202) ng/l ($P < 0.01$) at 6 months; and 58 (range 9.7 to 260) ng/l ($P = \text{NS}$) one year after closure.

Table 6. Diastolic and systolic parameters measured by 2D and 3D echocardiography at baseline and during the last follow-up and compared with those of controls. Values are given as median (range)

Diagn	ASD		PDA				P	value	6 mo f-u	P	value	P
	controls	baseline	P	12 mo f-u	P	controls						
N	51	24		21		36			26			
2D												
E	0.96	0.82	0.006	0.94	0.911	0.96	1.05	0.018	0.97	0.018	0.983	
(m/s)	(0.62-1.13)	(0.61-1.05)		(0.66-1.28)		(0.67-1.18)	(0.72-1.65)		(0.6-1.36)			
A	0.52	0.49	0.856	0.46	0.206	0.62	0.7	0.186	0.55	0.186	0.521	
(m/s)	(0.29-0.84)	(0.31-0.84)		(0.28-0.72)		(0.29-1.08)	(0.31-1.18)		(0.35-1.07)			
E/A	1.84	1.58	0.166	1.94	0.273	1.50	1.69	0.986	1.66	0.986	0.412	
	(0.98-3.5)	(0.96-2.88)		(1.44-3.29)		(0.98-3.5)	(0.87-3.55)		(0.94-3.12)			
Edt	123	98	0.018	147	0.015	109.5	106	0.639	130	0.639	0.046	
(ms)	(45-244)	(72-202)		(101-195)		(45-244)	(54-159)		(69-206)			
FS	38	36	0.417	36	0.227	40	38	0.056	37	0.056	0.091	
(%)	(28-56)	(17-50)		(29-45)		(33-50)	(29-51)		(27-45)			
EF	69	68	0.932	67	0.337	72	69	0.027	68	0.027	0.091	
(%)	(55-87)	(37-82)		(55-76)		(62-83)	(57-82)		(54-78)			
3D												
PFR	87.5	82.5	0.590	101.8	0.270	74.4	83.2	0.124	79.0	0.124	0.732	
(ml/s)	(46.0-282.3)	(28.4-319.1)		(41.0-329.3)		(20.0-166.1)	(22.8-165.3)		(38.0-151.9)			
TPFR	136	134	0.725	142	0.536	120.5	119.5	0.701	115.5	0.701	0.836	
(ms)	(43-528)	(36-396)		(12-796)		(10-272)	(10-314)		(12.0-408)			
PER	126.1	97.0	0.016	125.8	0.916	91.8	103.8	0.052	94.8	0.052	0.107	
(ml/s)	(51.7-308.4)	(40.1-259.7)		(59.2-290.6)		(24.5-176.9)	(53.7-211.6)		(69.6-178.3)			
EF	49	50	0.746	51	0.070	49	52	0.307	53	0.307	0.005	
(%)	(38-58)	(39-61)		(43-57)		(40-67)	(37-65)		(42-65)			

Abbreviations: A = atrial peak flow velocity, Edt = deceleration time of early diastolic flow, E/A = ratio mitral early peak flow velocity to atrial peak flow velocity, E = mitral early peak flow velocity, EF = ejection fraction, FS = fractional shortening, mo = months, PER = peak ejection rate, PFR = peak filling rate, TPFR = time to peak filling rate.

Table 6. Diastolic and systolic parameters measured by 2D and 3D echocardiography at baseline and during the last follow-up and compared with those of controls. Values are given as median (range)

Diagnosis	CoA	Multibrey nanism				
		controls	baseline	P value	12 mo f-u	P value
N	28	28	28	28	28	28
2D						
E (m/s)	0.95 (0.64-1.13)	1.07 (0.60-1.50)	0.005	1.17 (1.05-1.32)	<0.001	0.94 (0.60-1.21)
A (m/s)	0.63 (0.30-0.98)	0.83 (0.26-1.19)	0.003	0.73 (0.36-1.16)	0.052	0.46 (0.23-0.79)
E/A	1.49 (0.81-3.00)	1.21 (0.66-3.39)	0.069	1.57 (0.98-3.64)	0.942	1.88 (1.21-4.22)
Edt (ms)	98.5 (45-207)	113 (33-202)	0.507	116 (65-218)	0.475	84 (54-159)
FS (%)	37 (30-48)	41 (19-54)	0.056	43 (31-51)	0.006	33 (17-45)
EF (%)	69 (58-82)	72 (41-86)	0.066	75 (59-84)	0.007	63 (37-78)
3D						
PFR (ml/s)	82.5 (25.1-223.2)	86.2 (11.0-719.7)	0.768	124.6 (61.3-377.8)	0.010	83.7 (25.1-238.4)
TPFR (ms)	127.5 (10-291)	128.5 (37-650)	0.731	93 (50-365)	0.570	107.5 (48-288)
PER (ml/s)	101.5 (24.5-228.9)	112.3 (19.3-574.8)	0.682	142.1 (37.0-503.6)	0.070	91.6 (26.3-235.3)
EF (%)	59 (38-67)	48 (31-59)	0.403	55 (40-68)	0.031	66 (25-67)

Abbreviations: A = atrial peak flow velocity, Edt = deceleration time of early diastolic flow, E/A = ratio mitral early peak flow velocity to atrial peak flow velocity, E = mitral early peak flow velocity, EF = ejection fraction, FS = fractional shortening, mo = months, PER = peak ejection rate, PFR = peak filling rate, TPFR = time to peak filling rate.

Surgery vs catheterization

Finally, we compared the patients treated surgically to those treated with the percutaneous technique (I, Table III). In the surgical subgroup, ASD diameter was larger. No other differences existed between these subgroups prior to ASD closure.

In 2D echocardiography, in both subgroups, the RV end-diastolic dimension was larger than in controls even a year after closure. The increase in end-diastolic dimension and volume of LV was slower in the surgical subgroup but at the end of the follow-up, neither group differed from controls.

In averaged 3D time-volume curves of LV, normalization took place later in the surgical subgroup than in the patients treated percutaneously (I, Fig. 3A and 3B). After percutaneous closure, most changes in patients took place during the first month after the procedure, whereas patients operated on did not reach the control level during one-year follow-up.

Differences between the surgical and percutaneous subgroups and the controls were also apparent in levels of ANPN and proBNP (I, Table III). In the surgical subgroup, levels of natriuretic peptides remained higher than in controls throughout the one-year follow-up. In patients with percutaneous closure, they reached the levels of the control group by the end of that year.

7.2. Left ventricular volume overload in patients with PDA (II)

Transcatheter closure of the PDA was carried out in 33 children. Seven children with the Amplatzer device and 19 children with a coil completed the 6-month follow-up. During the follow-up, no residual shunts were visible in the children with PDAs closed with an Amplatzer device. Two children with PDAs occluded with a coil had minimal residual shunts at the time of the 6-month follow-up.

Table 7A. Serum levels of N-terminal pro-brain natriuretic peptide (proBNP) (ng/l) in patients and in controls. Values are expressed as median (range).

Subjects	Baseline proBNP				Last follow-up proBNP				P value as compared with controls	P value as compared with baseline
	Age median (range) years	N	median	range	P value as compared controls	N	median	range		
ASD pts	6.9 (2.3-18.5)	24	85	11-245	0.006	21	58	9.7-260	0.343	0.164
ASD cath		17	79	11-245	0.105	14	52.5	19-142	0.708	0.221
ASD op		7	90	72-181	0.002	7	97	49-260	0.015	0.499
controls	6.9 (2.5-15.6)	51	59	21-139						
CoA pts	3.50 (0.01-19.02)	28	113	5-35001	0.057	13	65	32-309	0.923	0.015
controls	4.19 (0.07-14.12)	28	72	26-230		23	54	26-157		
						>0.5				
Mulibrey pts	6.8 (0.4-15.9)	26	289	18-9170	0.001	v	576	17-7597	<0.001	0.859
controls										
PDA pts	6.8 (0.3-15.6)	26	54	26-139						
Controls	2.6 (0.9-10.6)	33	141	31-974	0.001	26	78.5	21-480	0.628	0.007
	3.3 (0.2-10.7)	36	72	27-321						

ANPN = N terminal pro-atrial natriuretic peptide; ASD = atrial septal defect; CoA = coarctation of the aorta; PDA = patent ductus arteriosus; proBNP = N-terminal pro-brain natriuretic peptide; pts = patients

Table 7B. Serum levels of N-terminal proatriopeptide (ANPN) (nmol/l) in patients and in controls. Values are expressed as median (range).

Subjects	Age median (range) years	Baseline ANPN			Last follow-up ANPN				P value as compared with controls	P value as compared with controls	P value as compared with baseline
		N	median	range	N	median	range				
ASD pts	6.9 (2.3-18.5)	24	0.43	0.11-1.40	21	0.31	0.10-0.70				
ASD cath		17	0.47	0.11-1.40	14	0.31	0.10-0.53	0.034	0.281	0.014	
ASD op		7	0.33	0.15-0.60	7	0.31	0.26-0.70	0.012	0.012	0.002	
controls	6.9 (2.5-15.6)	51	0.28	0.10-0.55						0.600	
CoA pts	3.50 (0.01-19.02)	28	0.53	0.16-16.30	13	0.38	0.09-0.83			0.060	
controls	4.19 (0.07-14.12)	28	0.35	0.15-1.20	23	0.30	0.15-0.61				
					>0.5y						
Mulibrey pts	6.8 (0.4-15.9)	26	0.54	0.04-4.7	10	1.02	0.17-6.30	< 0.001	< 0.001	0.263	
controls	6.8 (0.3-15.6)	26	0.28	0.09-0.72							
PDA pts	2.6 (0.9-10.6)	33	0.39	0.21-1.21	26	0.38	0.14-0.58	0.307	0.307	0.057	
Controls	3.3 (0.2-10.7)	36	0.31	0.10-0.77							

ANPN = N terminal pro-atrial natriuretic peptide; ASD = atrial septal defect; CoA = coarctation of the aorta; PDA = patent ductus arteriosus;
proBNP = N-terminal pro-brain natriuretic peptide; pts = patients

In cardiac catheterization, prior to PDA closure the systolic, diastolic, and mean pressures in the pulmonary artery measured a median 22 (range 16 to 45) mm Hg, 10 (range 6 to 20) mm Hg, and 15 (range 11 to 25) mm Hg, respectively. The LV end-diastolic pressure measured 7 (range 3 to 18) mm Hg. Aortic pressures increased significantly after PDA closure (**II**, Figure 3). Prior to closure, systolic, diastolic, and mean pressures in the aortic arch measured a median 87 (range 65 to 107) mm Hg, 48 (range 26 to 61) mm Hg, and 68 (range 50 to 80) mm Hg. After closure, the systolic, diastolic, and mean pressures in the aortic arch measured a median 99 (range 64 to 136) mm Hg, 58 (range 40 to 74) mm Hg, and 77 (range 52 to 100) mm Hg ($P < 0.001$ for each). In angiography, the smallest diameter of the PDA measured a median 1.5 (range 0.9 to 3.6) mm. In the patient subgroup with a normal-sized LV, the PDA measured 1.4 (range 0.9 to 3.6) mm. The smallest diameter of the PDA correlated with LV diastolic volume adjusted to BSA as measured by 2D echocardiography ($r = 0.601$, $P < 0.001$), z score of LV diastolic diameter ($r = 0.640$, $P < 0.001$), and LV end-diastolic volume adjusted to BSA measured by 3D echocardiography ($r = 0.382$, $P < 0.05$).

At baseline, in chest X-ray, cardiothoracic ratio measured a median 0.52 (range 0.44 to 0.71). Three patients had cardiothoracic ratios of more than 0.60. After PDA occlusion, all patients were asymptomatic with no signs of congestive heart failure. In chest X-ray, cardiothoracic ratio measured a median 0.50 (range 0.44 to 0.73) ($P < 0.01$ as compared to baseline). In one patient, the cardiothoracic ratio was still more than 0.60. However, in echocardiography, the z score of her LV end-diastolic diameter was -1.0 SD.

In 2D echocardiography, LV end-diastolic (**II**, Fig. 1A) and systolic volumes adjusted to BSA were larger in the patient group than in the control group (**II**, Table 2) at baseline (Table 5). The median z score of LV end-diastolic diameter was greater in patients ($P = 0.002$). It was abnormal (>2 SD) in five (15%) patients with PDA prior to PDA closure and in none in the control group. The mitral E wave was higher in the patient group. The other indices of diastolic function (A wave, the E/A ratio, the Evti and Avti, or Evti/EAvti, or deceleration rate of E wave) did not differ from those of the control group. Left ventricular FS and EF were lower in the patient group (**II**, Table 2). One day after the PDA occlusion, differences in end-diastolic (**II**, Fig. 1A) and systolic volumes as well as the difference in LV EF between the PDA group and control group remained significant in 2D echocardiography. However, 6 months after PDA occlusion, LV end-diastolic (**II**, Fig. 1A) and systolic volumes had decreased significantly as compared to baseline and did not differ from those in the control group. The z score of LV end-diastolic diameter was 0.0 (range -2.0 to 1.75) SD ($P =$ NS as compared with the control group). The difference in E wave of the mitral flow seen at

baseline between groups had disappeared. The deceleration rate of the early diastolic flow was now lower than at baseline and did not differ from that in the control group (Table 6 and **II**, Table 2).

In 3D echocardiography, the LV end-diastolic and systolic volumes adjusted to BSA were larger in the PDA group (Table 5), with no differences in diastolic or systolic indices of LV function between patients and controls. On the first day after occlusion of PDA, the LV end-diastolic volume adjusted to BSA remained larger and the PER was higher in the PDA group. After 6 months of follow-up, no differences appeared between groups in LV end-diastolic (**II**, Fig. 1B) and systolic volumes adjusted to BSA (**II**, Table 2). No differences were evident in diastolic indices of LV function between patients and controls, but the EF was higher in the patient group.

Serum levels of natriuretic peptides were higher in the patient group at baseline (Table 7), and on the first day after occlusion, natriuretic peptides remained higher. The serum concentration of proBNP had even increased to 192 (range 17 to 1182) ng/l ($P < 0.001$ as compared with controls, $P = 0.013$ as compared with baseline). The ANPN concentration measured 0.41 (range 0.16 to 1.13) nmol/l ($P = 0.018$ as compared with controls, $P = \text{NS}$ as compared with baseline). At the 6-month follow-up, serum concentrations of proBNP and ANPN did not differ from those in the control group (Table 7, **II**, Fig. 2A and B).

Within the PDA group, significant changes appeared in both diastolic and systolic indices of LV function and in LV size by 2D echocardiography 6 months after PDA occlusion as compared to baseline (**II**, Table 2): The E, the A, and deceleration rate of the early diastolic flow were lower than before the procedure. LV end-diastolic and systolic volumes adjusted to BSA decreased significantly during the 6-month follow-up. Similarly, at the time of the last follow-up, the level of proBNP was significantly lower than before the procedure and did not differ from that in the control group (**II**, Fig.2).

Finally, even in the subgroup of 28 with normal LV end-diastolic dimensions ($\leq +2\text{SD}$) at baseline, end-diastolic and systolic volumes adjusted to BSA were larger and levels of proBNP and ANPN higher at baseline than in the control group. All these differences had disappeared by the time of the last follow-up (**II**, Figure 2).

7.3. Left ventricular pressure overload in patients with CoA (III)

At baseline, the study group comprised 28 patients with CoA and 28 matched controls; systolic and diastolic blood pressures were higher in the patients. Systolic and diastolic blood pressure measured a median 123 (range 91 to 161) mm Hg and 67 (range 42 to 96) mmHg, respectively, in the CoA group and a median 101 (range 76 to 123) mm Hg ($P < 0.001$) and 59 (range 43 to 72) mm Hg ($P < 0.01$) in controls. The systolic arm-leg blood pressure gradient in the patient group measured a median 33 (range 14 to 57) mm Hg.

In 2D echocardiography, the smallest diameter of CoA segment measured a median 4.1 (range 1.6 to 13.1) mm. The end-diastolic diameter of the LV was larger in the patient group, with no differences between groups in z score of end-diastolic diameter of the RV. The z scores of the end-diastolic thicknesses of the interventricular septum and LV posterior wall were higher in patients (Table 5), with no differences between patients and controls in the indices of LV systolic function (Table 6).

In Doppler echocardiography of the mitral inflow signal, the E wave, the A wave, and the A/vti were all higher in the patient group (Table 6). The other indices of diastolic function did not differ from those in the control group.

In 3D echocardiography, no significant differences appeared in any of the parameters between patients and controls at baseline. Serum levels of ANPN were higher in the patient group, with no differences between groups in the levels of proBNP (Table 7).

In the 11 patients undergoing percutaneous angioplasty of the stenosed segment, the invasive blood pressure gradient across the CoA segment measured a median 26 (range 17 to 52) mm Hg before and 10 (range 0 to 16) mm Hg ($P = 0.003$) after the procedure. In angiography, the smallest diameter of the CoA segment measured a median 5.0 (range 2.5 to 9.0) mm before and 11.0 (range 4.4 to 17.0) mm ($P = 0.003$) after dilatation. The CoA gradient correlated inversely with diameter of the CoA segment ($r = -0.658$, $P = 0.003$).

A total of 17 patients underwent surgical repair, 16 children with resection and end-to-end anastomosis, and one with angioplasty with a tube prosthesis. Length of hospital stay was a median one day (range 1 to 8 days) for patients treated with percutaneous dilatation and 6 (range 5 to 20)

days for those repaired surgically. No mortality was associated with percutaneous or surgical treatment.

Follow-up

Of the 28 patients examined prior to repair, 15 completed the one-month follow-up: 11 of them had native CoA and 4 had reCoA. Nine children were treated with surgery, and six with balloon dilatation. Thirteen children completed the 6- and the 12-month follow-up (**III**, Table 2).

Prior to repair, one child was on medication for hypertension. After repair, five patients were on medication: four for hypertension, and one for LV dysfunction. Antihypertensive medication was discontinued before the first follow-up visit for one patient and after the first visit for three. After one month's follow-up visit, the only patient on medication was the one with left ventricular dysfunction which gradually improved, and she was weaned off medication by the end of the one-year follow-up.

The systolic arm-leg blood pressure gradient measured a median 30 (range 14 to 56) mm Hg at baseline, but had decreased to a median 0 (range 0 to 21) mm Hg ($P = 0.001$) by the time of the first follow-up visit. The gradient measured a median 5 (range 0 to 16) mm Hg ($P = 0.001$) 6 months, and 0 (range 0 to 12) mm Hg ($P = 0.001$) one year after repair.

In 2D echocardiography, the smallest diameter of the CoA segment measured a median 3.0 (range 1.6 to 11.2) mm before treatment, and a median 9.1 (range 3.4 to 14.3) mm ($P = 0.013$) one month, 9.8 (range 6.1 to 17.1) mm 6 months ($P = 0.002$), and 7.9 (range 6.0 to 14.4) mm ($P = 0.006$) 12 months after repair.

At baseline, the z score of end-diastolic diameter of LV was higher in patients, but it showed no significant decrease during follow-up. No difference was evident between groups in the z score of end-diastolic diameter of RV. That of the RV in the patient group increased during follow-up (**III**, Table 2). At baseline, the z scores of end-diastolic thicknesses of the interventricular septum and LV posterior wall were higher than in controls. They decreased for up to 6 months after the procedure but increased again to initial levels by the end of the one year follow-up. (Table 2, Figure 1). No significant changes were evident during the one-year follow-up in the indices of LV systolic function as measured by M-mode echocardiography (**III**, Table 2).

In Doppler echocardiography of the mitral inflow signal, the E and A waves and the Avti were all higher in patients at baseline, with no changes taking place in indices of LV diastolic function during the first month after the procedure. After that, the Evti and EAvti of mitral flow increased significantly as compared with baseline (**III**, Table 2).

In 3D echocardiography, LV EF increased during the follow-up (**III**, Table 2), and at the end of follow-up, LV peak filling rate was higher than in controls (**III**, Table 2).

The serum levels of natriuretic peptides decreased significantly during follow-up (**III**, Table 2).

7.4. Cardiac dysfunction in children with Mulibrey nanism (IV)

Nine children with Mulibrey nanism were on growth hormone treatment. Of the five patients severely symptomatic, with shortness of breath and decreased exercise tolerance, four were treated with diuretics (furosemide, hydrochlorothiazide, and/ or spironolactone) for cardiac failure. One received flecainide and bisoprolol for Wolf-Parkinson-White syndrome and another one sotalol for atrial flutter; three additional children complained of decreased exercise tolerance as compared with their peers; 18 children were asymptomatic. Six had undergone pericardiectomy 1 to 10 years earlier at a median age of 2.3 (range 0.5 to 11.3) years. One had minimal patent ductus arteriosus. The three most symptomatic children were 0.4, 1.1, and 3.1 years old.

During the echocardiographic examination, no difference emerged in heart rate between patients and the control group, being a median 91 (range 58 to 143) and 84 (range 55 to 139), respectively (P = NS).

Two-dimensional echocardiography

In 2D echocardiography, z scores of end-diastolic thickness of the interventricular septum and LV posterior wall in the patient group were higher (Table 5). They measured a median 1.25 (range -1.00 to 2.75) SD and 0.25 (range -1.00 to 3.50) SD in the Mulibrey group, and 0.125 (range -1.25 to 1.50) SD (P < 0.01) and -0.375 (range -2.00 to 1.75) SD (P < 0.05) in the control group (**IV**, Fig.1). Evti and Avti, as well as the EAvti, were shorter in the patient group than in controls (**IV**, Table 2). In the other indices of diastolic LV function: E, A, E/A ratio, Evti/EAvti, or deceleration rate of early diastolic flow, no differences were evident between patients and controls (Table 6).

In the children with Mulibrey nanism the size of the left atrium was larger. The LA/Ao ratio measured a median 1.8 (range 1.4 to 2.5) for patients and 1.3 (range 1.0 to 1.7) for controls ($P < 0.001$). The LA/ Ao ratio correlated with several indices of diastolic LV function as measured by 2D echocardiography: EAvti ($r = -0.434$, $P < 0.01$), Evti ($r = -0.341$, $P < 0.05$), and DT of mitral E wave ($r = -0.379$, $P < 0.05$). LA/Ao ratio also correlated with 3D indices of myocardial function: TPFR ($r = -0.421$, $P < 0.01$) and PER ($r = -0.368$, $P < 0.05$). LV contractility (FS and EF) was lower in the patient group (**IV**, Table 2).

Three-dimensional echocardiography

In 3D echocardiography, the LV in the Mulibrey group was smaller. The LV end-diastolic and end-systolic volumes adjusted to BSA measured a median 51.9 (range 33.3 to 73.4) ml/m² and 26.6 (range 16.2 to 37.2) ml/m² in the Mulibrey group, and 59.7 (range 37.6 to 87.6) ml/m² ($P < 0.05$) and 29.3 (range 21.1 to 46.8) ml/m² ($P < 0.01$) in controls. In the indices of diastolic function (PFR and TPFR), no difference appeared between groups. Of the indices of systolic function, PER was lower in the Mulibrey group (Table 6 and **IV**, Table 2) with no difference in 3D EF between groups.

Natriuretic peptides

Concentrations of serum natriuretic peptides were higher in the patient group (Table 7 and **IV**, Fig. 2A and B). The ANPN measured a median 0.54 (range 0.04 to 4.7) nmol/l in the Mulibrey group and 0.28 (range 0.09 to 0.72) nmol/l in the controls ($P < 0.01$). The proBNP measured a median 289 (range 18 to 9170) ng/l in patients with Mulibrey nanism and 54 (range 26 to 139) ng/l in controls, ($P < 0.01$).

Based on the normal range determined in our unit, in the group with Mulibrey nanism, 13 children had ANPN levels and 17 their proBNP levels above the normal range. Of 26 patients, 11 (41%) had both values above the normal range; only 8 (31%) had both values within normal limits, and of these 8, 5 were asymptomatic; one of the asymptomatic patients with normal serum levels of natriuretic peptides had undergone pericardiectomy.

Pericardiectomy had been performed on 6 children with Mulibrey nanism, but 20 remained unoperated. Despite a tendency to higher serum levels of ANPN and proBNP in patients treated with pericardiectomy, this difference did not reach significance: ANPN levels measured a median 0.53 (range 0.04 to 2.50) nmol/l in unoperated patients and 0.83 (range 0.31 to 4.70) nmol/l in the pericardiectomy group ($P = \text{NS}$). ProBNP levels measured a median 298 (range 18 to 2402) ng/l in

the unoperated group and 431 (range 58 to 9170) ng/l after pericardiectomy ($P = \text{NS}$). The subgroups with and without pericardiectomy did not differ in echocardiographic indices of LV diastolic and systolic function. In the patients treated with pericardiectomy, the interventricular septum was thicker. The z score of the thickness of the interventricular septum measured a median 0.75 (range -1.00 to 2.75) SD in the group without pericardiectomy and 1.50 (range 1.25 to 2.25) SD in the group with pericardiectomy ($P < 0.05$).

We compared the children with and without growth hormone therapy and found no difference in the end-diastolic thicknesses of the interventricular septum or LV posterior wall. Comparison of patients with and without symptoms showed differences in 2D and 3D echocardiography and in levels of natriuretic peptides (**IV**, Table 3). In 2D echocardiography, the EAvti and the Evti of mitral inflow signal in those with symptoms were shorter. In 3D echocardiography, the LV end-diastolic volume adjusted to BSA was smaller, and PER and PFR lower in symptomatic patients; serum proBNP concentration was higher in symptomatic patients.

Within the group with Mulibrey nanism, during the follow-up of 6 to 12 months, no significant changes occurred, neither in the levels of natriuretic peptides nor in any of the parameters measured in 2D and 3D echocardiography.

7.5. Serum levels of ANPN and proBNP (I-IV)

Serum levels of ANPN and proBNP at baseline and at the last follow-up visit are shown in Table 7. Study III, included age-matched controls at baseline and excluded controls aged less than 6 months from comparison at the last follow-up visit. All the other studies used the same controls at baseline and during follow-up.

In our unit, we have determined the normal values of ANPN and proBNP in children aged more than 6 months among a group of 64 healthy children. The normal range (mean \pm 2SD) for serum ANPN concentration is 0.13 ± 0.26 nmol/l and for serum proBNP concentration 32 ± 63 ng/l. The measurable range for our assays was for ANPN 0.1 to 5.0 nmol/l and for proBNP 5 to 35 000 ng/l. In statistical analysis, an ANPN concentration of 0.09 nmol/l served for values below 0.1 nmol/l and a proBNP concentration of 4.9 ng/l for values less than 5 ng/l, and that of 35 001 ng/l for values higher than 35 000 ng/l.

Correlation of natriuretic peptide levels with echocardiographic measurements

In Study **I**, serum levels of ANPN and proBNP correlated with 2D echocardiographic indices of diastolic LV function and systolic LV size: DT of the E wave ($r = -0.676$, $P < 0.001$, and $r = -0.473$, $P = 0.020$, respectively) and the deceleration rate of E wave ($r = 0.738$, $P < 0.001$, and $r = 0.571$, $P = 0.004$), and the end-systolic LV volume ($r = 0.417$, $P = 0.043$, and $r = 0.465$, $P = 0.022$). No correlation appeared between levels of natriuretic peptides and end-diastolic dimensions of RV or of LV, or the Qp/Qs ratio. The Qp/Qs ratio correlated with size of ASD as measured by transesophageal echocardiography ($r = 0.528$, $P = 0.024$), with distended diameter of the ASD ($r = 0.711$, $P = 0.001$), and with the z score of the end-diastolic diameter of RV ($r = 0.573$, $P = 0.016$).

In Study **II**, levels of proBNP correlated with the z score of LV end-diastolic diameter ($r = 0.388$, $P = 0.025$), and end-diastolic LV volume adjusted to BSA by 2D echocardiography ($r = 0.404$, $P = 0.020$), but not with the smallest diameter of the PDA.

In patients with CoA (Study **III**), prior to repair in 28 eight patients, a negative correlation appeared between serum levels of ANPN and proBNP and measurements in 2D and Doppler echocardiography: diameter of the CoA segment ($r = -0.676$, $P < 0.001$; and $r = -0.713$, $P < 0.001$, respectively) and indices of diastolic LV function: ratio E/A ($r = -0.581$, $P = 0.001$; and $r = -0.480$, $P = 0.010$) and E DT ($r = -0.639$; $P < 0.001$; and $r = -0.693$, $P < 0.001$).

Similarly, a negative correlation emerged between levels of ANPN and proBNP and LV size and indices of LV diastolic and systolic function in 3D echocardiography: end-diastolic volume ($r = -0.724$, $P < 0.001$; and $r = -0.714$, $P < 0.001$, respectively), PFR ($r = -0.850$, $P < 0.001$; and $r = -0.762$, $P < 0.001$), and PER ($r = -0.820$, $P < 0.001$; and $r = -0.739$, $P < 0.001$).

In patients with Mulibrey nanism (Study **IV**), levels of ANPN correlated with indices of LA size and diastolic LV function in 2D and 3D echocardiography: LA/Ao ratio ($r = 0.480$, $P < 0.01$), EAvti ($r = -0.462$, $P < 0.01$), Evti ($r = -0.350$, $P < 0.05$), DT of E wave ($r = -0.367$, $P < 0.01$), TPFR ($r = -0.390$, $P < 0.01$), and PER ($r = -0.435$, $P < 0.01$).

Levels of proBNP also correlated with indices of LA size and diastolic LV function in 2D echocardiography: LA/Ao ratio ($r = 0.541$, $P < 0.001$), EAvti ($r = -0.445$, $P < 0.01$), Evti ($r = -0.434$, $P < 0.01$), the DT of E wave ($r = -0.450$, $P < 0.01$), and the deceleration rate of the E wave ($r =$

0.430, $P < 0.01$). Additionally, levels of proBNP correlated with indices of diastolic LV function and size of the LV in 3D echocardiography: PFR ($r = -0.420$, $P < 0.01$), PER ($r = -0.687$, $P < 0.001$), end-diastolic LV volume adjusted to BSA ($r = -0.484$, $P < 0.001$), and end-systolic LV volume adjusted to BSA ($r = -0.500$, $P < 0.001$).

8. DISCUSSION

8.1. Volume overload of right ventricle (I)

In this prospective study, significant differences existed in echocardiography at baseline between patients with ASD and controls. In the patient group, RV end-diastolic diameter was larger and LV end-diastolic and end-systolic volumes smaller, a finding in concordance with an angiographic study on ASD patients demonstrating increase in RV volume, output, and distensibility with normal RV function but a decrease in LV volume, EF, and output (Mathew et al. 1976).

The size of RV decreased after ASD closure but remained larger than in controls even after a one-year follow-up both in children treated surgically and in those treated percutaneously. Persistence of RV dilatation after surgical ASD repair has been reported for both pediatric and adult patients (Pearlman et al. 1978, Bjorkhem and Lundstrom 1980, Meyer et al. 1982, Groundstroem et al. 1999, Groundstroem et al. 2003). After transcatheter closure, some reduction in (Meijboom et al. 1993, Pedra et al. 2000, Du et al. 2001, Kort et al. 2001, Veldtman et al. 2001, Yew and Wilson 2005) or even normalization of RV size has taken place during follow-up (Shaheen et al. 2000, Kort et al. 2001, Giardini et al. 2004, Bolz et al. 2005).

At baseline, end-diastolic volume of LV in our patients was smaller than in controls in 2D and 3D echocardiography, with a similar finding in angiographic studies (Popio et al. 1975, Mathew et al. 1976). In 2D and 3D echocardiography in both treatment groups, end-diastolic and end-systolic volumes of LV increased after ASD closure. Similar increases, in end-diastolic diameter (Bonow et al. 1981) and volume of LV after both surgical and percutaneous ASD closure, have been demonstrated earlier in pediatric and adult populations (Shaheen et al. 2000, Du et al. 2001, Salehian et al. 2005).

In RV volume overload, septal motion toward the LV cavity takes place during the end-diastole and may cause a decrease in the LV ejection fraction (Louie et al. 1995, Walker et al. 2004). In this study, however, LV contractility (FS, EF) did not differ from that of controls before or after ASD closure in either treatment group. In the averaged time-volume curves of the LV, changes in end-systolic volumes were evident, especially in the subgroup undergoing percutaneous closure, whereas changes towards normality in the surgical subgroup took place more slowly. This may be in part due to an initially larger size of ASD. Studies have reported an increase in diastolic but no

change in systolic LV dimensions after ASD closure and therefore an increased ejection fraction (Du et al. 2001, Giardini et al. 2004, Walker et al. 2004, Salehian et al. 2005). The myocardial performance index of both ventricles has been shown to improve after transcatheter ASD closure (Salehian et al. 2005).

In some studies, radionuclide and angiographic PFR and PER have been normalized by end-diastolic volume or by stroke volume (Lee et al. 1989, Satoh et al. 1996, Arsos et al. 2002). Normalized angiographic PFR is lower in adult patients with a large ASD than in controls. In our study, we chose not to use normalized values for PFR or PER. PFR was similar in our patients and controls; PER was lower than in controls at baseline but reached control level one year after closure. The increase in PER during the one-year follow-up may be due to increased preload, to remodeling of LV after cessation of RV volume overload, or to normalization of septal motion (Hart et al. 2004, Walker et al. 2004).

In our study, ventricular interdependence was demonstrated as a left-to-right shunt through the ASD, causing a volume overload of the RV and a decreased preload of the LV and thereby decreased mitral inflow velocities. At baseline, that the E and E/A ratio, Evti, and EAvti were significantly lower than in controls may be due to the reduced preload resulting from shunting through the ASD but probably not to the diastolic dysfunction of the LV, since no other indices of diastolic function of LV in 2D and 3D echocardiography differed from those of control patients. After closure, all the diastolic indices of the LV function were similar to those in controls.

8.2. Volume overload of left ventricle (II)

Percutaneous occlusion of PDA was a safe and effective procedure with no complications. Only two children had a hemodynamically insignificant minimal residual shunt 6 months after the procedure.

At baseline, in both 2D and 3D echocardiography, the end-diastolic and systolic volumes adjusted to BSA were larger in the PDA group, a difference that disappeared after closure, even in those patients with normal-sized LVs. This is in concordance with a study on full-term infants using a biplane Simpson method (Takahashi et al. 1996). The smallest diameter of the PDA correlated with LV end-diastolic volume adjusted to BSA. Of the indices of LV diastolic function in 2D echocardiography, the mitral E wave was higher in our patients than in controls. PFR, a sensitive

index of diastolic function in 3D echocardiography (Zeidan et al. 2002), was higher in our PDA patients at baseline, but this difference failed to reach significance. These findings reflect the increased preload at baseline. In 2D echocardiography, at the time of the last follow-up, 6 months after PDA closure, the mitral E wave, A wave, and the deceleration rate of the E wave had decreased compared to baseline. This may reflect decreased flow through the mitral valve, decreased sympathetic activity, and normalized LV compliance.

In one study, the systolic and diastolic blood pressures increased after coil occlusion of PDA, leading to increased flow volume and maximum peak flow velocity in the left anterior descending coronary artery (Harada et al. 2004). Similarly, in our study, significantly higher aortic systolic, diastolic, and mean pressures were measured in cardiac catheterization after PDA closure than at baseline.

No correlation has been found between the presence of a murmur and the size of the PDA (Bennhagen and Benson 2003). This may be due to differences in direction of ductal flow. The size and the shape of an elastic PDA and the amount of shunting through it may vary and cause a more significant volume overload of the LV than anticipated. All our patients had either a systolic or a continuous murmur. Our follow-up data suggest that even a PDA which appears small by echocardiography may cause significant LV volume overload. It may also predispose the patient to endarteritis (Balzer et al. 1993, Sadiq et al. 2004). Even in the subgroup of patients with a normal-sized LV, the LV size and the levels of natriuretic peptides decreased after PDA closure. Patients with small PDAs thus require careful evaluation. They may need to be followed up and subsequently considered as candidates for PDA closure.

8.3. Pressure overload of left ventricle (III)

Coarctation of the aorta is a lifelong disease process. Patients with CoA are at risk for recurrent CoA, arterial hypertension, premature atherosclerotic disease, heart failure, cerebrovascular accidents, rupture of an aortic aneurysm, or sudden death, even after successful treatment (Cohen et al. 1989, Meyer et al. 2005, Rosenthal 2005). Aortic remodeling can occur in patients after angioplasty for CoA (Rao and Carey 1989). In our study, after percutaneous and surgical repair, a significant increase in the diameter of the CoA segment and reduction in the pressure gradient across the coarctation occurred. Risk for reCoA after surgery in the neonatal period has been up to 19%, and after the neonatal period up to 3% (Pfammatter et al. 1996, Pearl et al. 2004). Risk for

reintervention after balloon dilatation has been up to 80% in the neonatal and infant period and up to 13% in children aged over one year (Rao et al. 1996, Ovaert et al. 2000). None of our patients developed reCoA during their one-year follow-up.

Adult populations have shown increased morbidity and mortality due to arterial hypertension and atherosclerotic disease despite successful CoA repair (Cohen et al. 1989, Meyer et al. 2005). In children, prevalence of arterial hypertension has also been detectable after CoA repair (O'Sullivan et al. 2002, Meyer et al. 2005). In our study, at baseline, systolic blood pressure was higher in patients than in control children, but after repair, no differences were detectable in systolic or diastolic blood pressures. In other studies, in children with no residual obstruction after CoA repair, prevalence of arterial hypertension was 21% by casual blood pressure measurement and 54% by 24-hour blood pressure measurement (O'Sullivan et al. 2002, Meyer et al. 2005).

Although the thickness of the interventricular septum and the LV posterior wall were within normal limits in most patients, as a group they differed from controls at baseline. The thickness of the interventricular septum decreased for up to 6 months after the procedure. However, one year after repair, it had again increased, although the patients were normotensive at rest. Animal studies suggest that after coarctation repair, humoral factors may be involved in the cardiac hypertrophic response (Iso et al. 1997). Systolic and diastolic hypertension in ambulatory blood pressure measurement, impaired flow-mediated vasodilatation, and increased thicknesses of the intima and media of the carotid artery can occur years after CoA repair in children and young adults (Gardiner et al. 1994, de Divitiis et al. 2003, Meyer et al. 2005).

Evaluation and follow-up of LV diastolic function in patients with CoA is important, since diastolic dysfunction may precede systolic dysfunction in patients with heart failure (Auslender 2000, Zile and Brutsaert 2002a, b). Because diastolic indices of LV function are age- and heart-rate-dependent (Arsos et al. 2002), we chose age- and gender-matched controls. In our study, differences were detectable in the indices of diastolic LV function between patients and controls at baseline. That increased afterload causes impaired relaxation, and decreased compliance of LV (Grodecki and Klein 1993, Mottram and Marwick 2005) explains why the peak velocities of the E and A waves of mitral inflow were higher at baseline in our patients than in controls. Similar findings have appeared in patients late after CoA repair (Moskowitz et al. 1990, Sigurdardottir and Helgason 1997). Hypertrophy of the interventricular septum and LV posterior wall may be in part responsible for decreased LV compliance.

In our patients, the z score of the RV end-diastolic diameter increased during follow-up due to remodeling of the ventricles after cessation of LV pressure overload. No significant change in LV volume occurred during follow-up, and during the follow-up, although no changes in LV contractility were evident in 2D echocardiography, LV contractility in 2D- and 3D echocardiography was higher in patients with CoA after one year. In 3D echocardiography, EF increased after repair. Similar findings with hyperdynamic and hypertrophied LV have been reported several years after surgery for CoA, suggesting that after CoA repair some degree of LV remodeling takes place, but the LV geometry and hypertrophy do not normalize entirely (Crepaz et al. 2005).

8.3. Cardiac involvement in Mulibrey nanism (IV)

Our study population covered 87% of all the children in Finland diagnosed with the rare inherited disease Mulibrey nanism. This disease affects multiple organs and causes severe growth retardation. Life expectancy is influenced by heart manifestations including constrictive pericarditis and restrictive cardiomyopathy (Lipsanen-Nyman et al. 2003).

Because diastolic indices are dependent on heart rate and age (O'Leary et al. 1998, Mottram and Marwick 2005), we used age-matched controls; heart rate in both groups was similar. In children with Mulibrey nanism, we detected abnormalities in both diastolic and systolic LV function. Of the diastolic indices of LV function in 2D echocardiography, EAvti, Evti, and Avti were significantly shorter in patients than in controls. However, no difference existed between groups in E/A ratio, which may be due to pseudonormalization of the mitral flow in the course of the disease progress, and a combination of the features of restrictive and constrictive myocardial disease.

In these children, the fact that the LV posterior wall and interventricular septum were thicker and the LA larger than in controls is in concordance with reports on older patients (Lipsanen-Nyman et al. 2003). Both the increased thicknesses of the interventricular septum and LV posterior wall and the shorter time velocity integrals of mitral inflow may reflect impaired relaxation of the LV. Similar to the adult population, in most of our patients this abnormality in LV filling physiology failed to resolve after pericardiectomy. Even some of our youngest children were severely symptomatic despite treatment with cardiac medication and pericardiectomy. Our patients as a group differed from their controls in the parameters of systolic LV function, although 2D EF and

3D PER fell within normal limits in most patients. In adult patients, no difference has been found in systolic function between patients with Mulibrey nanism and controls (Lipsanen-Nyman et al. 2003). In our study, the 3D end-diastolic volume of LV in symptomatic patients was smaller, and PER and PFR lower.

In studies on patients with Mulibrey nanism, half the adult patients developed congestive heart failure during follow-up, and severe congestive heart failure, unresponsive to pericardiectomy, has occurred in young patients (Tuuteri et al. 1974, Lipsanen-Nyman et al. 2003). Although pericardial constriction has been the most common finding, myocardial involvement with hypertrophy and fibrosis is an essential component in this heart disease (Lipsanen-Nyman et al. 2003). These changes seem to appear in early childhood. In our patient population, a difference appeared in echocardiographic indices of diastolic function and in serum levels of natriuretic peptides between patients and controls, but no difference appeared in these indices between patients with and without pericardiectomy. This suggests that in children treated with pericardiectomy, in addition to constrictive pericarditis, myocardial restriction may be present. In our study, their clinical condition improved in four out of six patients undergoing pericardiectomy. We therefore recommend pericardiectomy for symptomatic patients with echocardiographic evidence of severe diastolic dysfunction with or without suspicion of thickened pericardium.

Significant variation seems to exist in the incidence, timing, and prognosis of myocardial involvement in Mulibrey nanism. Our three patients with the most severe symptoms were less than 4 years old. On the other hand, some of the older children were asymptomatic, with normal serum levels of natriuretic peptides. Significant differences were detectable both in 2D and 3D indices of LV function and in serum levels of natriuretic peptides between asymptomatic and symptomatic patients, suggesting restrictive physiology in the latter. During our follow-up of one year, disease progress was slow, with no significant hemodynamic changes.

8.4. Natriuretic peptides in children with and without congenital cardiac defects

Natriuretic peptides play an important role in maintaining hemodynamic stability. Measurement of serum levels of natriuretic peptides can differentiate heart disease from lung disease as a cause of dyspnea, in screening of cardiac dysfunction in an adult population, and in evaluation of risk for sudden death in pediatric patients with LV dysfunction (Dao et al. 2001, Berger et al. 2002, Hobbs et al. 2002, Lubien et al. 2002, Bettencourt et al. 2004, Dokainish et al. 2005, Mueller et al. 2005, Dokainish et al. 2006, Price et al. 2006). Levels of natriuretic peptides depend on loading conditions. Unlike Doppler measurements in 2D echocardiography, they are not heart-rate dependent, and thus are useful in evaluation of cardiac function in a pediatric population in which variation in heart rate is important. Little is known, however, about the effect of treatment of congenital heart disease on the levels of natriuretic peptides in children. The problems in several reports are small study population, large variation in heart defects, and lack of matched controls (Mir et al. 2002, Westerlind et al. 2004, Holmgren et al. 2005, Law et al. 2005).

In our study, ANPN levels decreased after ASD closure but remained higher than in controls 6 months after closure. After that, the levels were similar to those of controls in the subgroup with percutaneous closure but higher than in controls in the surgical subgroup. This may be in part due to the larger size of the ASD and the more significant RV volume overload in the latter (Kort et al. 2001), although we detected no correlation in this patient group between natriuretic peptide levels and end-diastolic diameters of RV or LV, size of ASD, or amount of shunt. Cardiopulmonary bypass may also play a role in the elevation of natriuretic peptide levels, since higher than normal ANPN concentrations have been reported years after surgical ASD repair (Iivainen et al. 2000, Groundstroem et al. 2003).

Similarly, serum levels of proBNP increased from baseline to the one-month follow-up in all ASD patients, perhaps due to increased volume into the LV after cessation of shunting through the ASD or, again, to the influence of cardiopulmonary bypass (Seghaye et al. 1997, Brancaccio et al. 2004, Costello et al. 2004, Weber et al. 2006). In patients treated percutaneously, proBNP levels had normalized by the 6-month follow-up, in concordance with earlier findings (Muta et al. 2002, Weber et al. 2006). After surgery, however, proBNP levels remained higher than in controls for up to one year. In adult patients, elevated BNP levels have been demonstrable years after cardiac surgery (Attenhofer Jost et al. 2002).

In our study on patients with PDA, levels of natriuretic peptides were significantly higher before PDA closure in patients than in controls. Serum levels of proBNP on the first day after PDA closure were higher than at baseline, probably due to anesthesia and excessive volume load caused by intravenous fluids and contrast media. Six months after this procedure, levels of natriuretic peptides showed no differences between the groups. Even in the subgroup of patients with normal-sized LVs at baseline, the decrease in the levels of natriuretic peptides was significant. Elevated proBNP levels seem to reflect volume overload of the LV even in asymptomatic patients with normal-sized LVs. In preterm infants, the magnitude of shunting through a PDA is the main determinant of plasma levels of natriuretic peptides (Holmstrom et al. 2001).

In the adult population, levels of BNP vary with hemodynamic state and can serve to reveal the effects of treatment (Maisel 2001). In pediatric patients, plasma concentrations of proBNP correlate well with clinical signs of heart failure (Mir et al. 2002). The plasma atrial natriuretic polypeptide concentrations correlate with hemodynamic measurements in children with congenital heart diseases (Kikuchi et al. 1987). In our study on patients with PDA, the proBNP levels correlated with LV end-diastolic volume.

Serum levels of ANPN were higher and that of proBNP had a tendency to be higher prior to repair in the whole group of CoA patients with and without follow-up than in controls, and levels decreased thereafter. However, no difference appeared in serum levels between the smaller study group of patients with follow-up and their matched controls. This is in concordance with the findings of one study on children with LV pressure overload having levels of natriuretic peptides almost equal to control levels (Holmgren et al. 2005). Based on our results, we recommend for a pediatric population that measurement of serum levels of natriuretic peptides be included in follow-up before and after treatment of CoA. These can serve as individual indicators of response to treatment and prove useful during follow-up.

In an adult population, elevation of plasma BNP is a hallmark of diastolic heart failure independent of ventricular hypertrophy (Yamaguchi et al. 2004). Another study has shown in adult patients that plasma levels of BNP are higher in restrictive cardiomyopathy than in constrictive pericarditis (Leya et al. 2005). In our study, plasma levels of both proBNP and ANPN in children with Mulibrey nanism were significantly higher than in controls. ProBNP concentration was above the normal range in two-thirds of the children with Mulibrey nanism; only one-third of the patients had both ANPN and proBNP concentrations within the normal range.

When the correlation between indices of diastolic LV function and levels of natriuretic peptides was studied in an adult population, deceleration time of the mitral E wave correlated with levels of BNP (Mottram and Marwick 2005). In other studies, levels of BNP have correlated with indices of systolic function (Yu et al. 1996). In all our studies, serum levels of natriuretic peptides correlated with several indices of diastolic and systolic LV function in 2D and 3D echocardiography.

In some studies, levels of the active part of the BNP hormone are measured, and in others, its inactive N-terminal fragment proBNP. BNP is more sensitive to acute hemodynamic changes, with levels increasing within 2 hours as a response to hemodynamic changes. Levels of proBNP increase more slowly, within 12 hours after stimulus (Rademaker and Richards 2005). Concentrations of serum levels of natriuretic peptides can be measured either from plasma or from serum. Each has specific range of normal values for each age-group (Nir and Nasser 2005).

8.6. Methodological considerations and limitations of the study

In this prospective study on pediatric patients, we evaluated hemodynamic changes in four different types of heart defects with a follow-up of up to one year. Number of patients decreased with longer follow-up. However, only a few prospective follow-up studies concern pediatric patients and even fewer have a follow-up after treatment for a specific lesion. In addition, little data are available on follow-up of patients by the methods used here.

Study **I** used a group of controls matched for age and BSA. In a pediatric patient population, gender distribution has little effect on hemodynamic parameters. We had age-, BSA-, and gender-matched controls in Studies **II** and **III**. Study **IV**, had age- and gender-matched controls, because severe growth retardation in Mulibrey nanism makes it impossible to match controls for both BSA and age. We chose to do this because heart rate and age are major determinants of diastolic function (Bu'Lock et al. 1995, Arsos et al. 2002, Mottram and Marwick 2005).

We used the so-called freehand 3D echocardiography system, which relies on the reconstruction of multiple 2D images. ECG gating was used, but this system made it impossible to use respiratory gating. Scanning of the plane took place if the heart rate was within ± 20 beats/min of the average. As the indices of diastolic function are heart-rate-dependent, the great variation in heart rate in small children may have had some effect on results. Our interobserver variability for LV end-diastolic and systolic diameter and LV end-diastolic and systolic volume measurements in M-mode

echocardiography was 3.1% (-0.41 ± 2.38), 3.1% (0.33 ± 1.3), 8.1% (0.58 ± 2.24), and 6.5% (-1.77 ± 7.46), respectively. This is in the same range as in a study in which interobserver variability for determination of end-diastolic volume of the LV by 2D echocardiography and 3D echocardiography measured 17.5% and 4.0%, respectively. In that study measurements for intraobserver variability were 17.3% and 3.2% (Chuang et al. 2000).

In our study, because 3D echocardiography was performed solely by one investigator, interobserver variability was not measured. Our intraobserver variability for measurements of LV end-diastolic and systolic diameter and LV end-diastolic and systolic volume in M-mode echocardiography was 2.2% (0.08 ± 2.58), 5.1% (0.49 ± 3.44), 5.3% (0.54 ± 10.98), and 12.0% (1.22 ± 7.44), respectively. For 3D diastolic and systolic LV volumes, it measured 9.5% (-0.33 ± 6.1) and 8.8% (-0.80 ± 10.74). The higher variability in this parameter may be due to the age of our patients, in whom breath-holding could not be used in data acquisition (Acar et al. 1998, Chuang et al. 2000).

For evaluation of LV diastolic function, we used Doppler echocardiography, but unfortunately, this method is dependent on loading conditions. Some evidence exists that if conventional Doppler echocardiography is combined with new methods such as tissue Doppler and color flow imaging, it is possible to get less load-dependent information on myocardial relaxation, LV compliance, and ventricular filling pressures (Oh et al. 2006). These methods were, however, unavailable at the time of our study. Doppler measurement of pulmonary venous flow can be examined as an index of LV diastolic function. In pulmonary veins, increased reversal flow can be seen in the presence of abnormalities in diastolic function (Mottram and Marwick 2005). Additionally, in constrictive pericarditis and restrictive cardiomyopathy, respiratory variation in mitral inflow signal and in pulmonary venous flow differs (Myers and Spodick 1999). This method is technically challenging and carries a risk for misinterpretation in small children with high respiratory rates (Hancock 2001) and was therefore not used in our study.

Left ventricular systolic function can be evaluated with Simpson's method by 2D echocardiography and with the Teichholz method by M-mode echocardiography. We chose the M-mode method for this purpose because the parameters of LV size obtained can be easily compared during the follow-up of the patients and in comparison with other children, other studies, and published normal values. With this method the shape of the LV is assumed to be cylindrical. It utilizes measurements of ventricular diameters to calculate volumes and function. It cannot be used in the presence of regional wall motion abnormalities or in distortion of the LV (Gutgesell 1985).

In this study, we also wanted to use 3D echocardiography for evaluation and follow-up of children before and after treatment for various loading conditions. The freehand method of 3D echocardiography we used is technically demanding because for data collection the probe needs to be rotated 180 degrees to acquire 9 image planes. Off-line post-processing of data is required for LV reconstruction. Today, real-time 3D echocardiography is available. With this method, data acquisition is faster, but postprocessing for LV function needs to be done on an off-line workstation as well (Kasliwal et al. 2005).

Because, concentration of natriuretic peptides is higher immediately after birth and decreases thereafter during the first 2 to 4 months (Weil et al. 1986, Matsuoka et al. 1988, Nir et al. 2004), in all our studies, we chose to have age-matched control children. In Table 7, control children aged less than 6 months are excluded from comparison with patients at the one-year follow-up.

9. CONCLUSIONS

1. During the one-year follow-up after ASD closure, RV size decreased but did not reach the control level either in children treated surgically or in those treated percutaneously. The size of the LV normalized after ASD closure, but the increase in LV size was slower in patients treated surgically. This may be due in part to the fact that ASD size was greater in surgical patients than in those treated percutaneously. Serum levels of ANPN and proBNP were elevated prior to ASD closure and increase further during the first month after the procedure. Levels decreased thereafter to control levels in patients treated with the percutaneous technique but not in those treated surgically. Despite successful treatment, ASD caused significant hemodynamic changes that persisted more than one year after closure. This hemodynamic improvement happened faster in children treated percutaneously than in those treated surgically.

2. Percutaneous occlusion of PDA is a safe and effective procedure. In children with PDA, LV size was increased prior to percutaneous closure and decreased thereafter. The smallest diameter of the PDA correlated with LV end-diastolic volume. Aortic systolic, diastolic, and mean pressures were higher after PDA closure than at baseline. Changes in LV volume and function caused by PDA disappeared by 6 months after percutaneous closure. Even the children with normal-sized LV benefited from the procedure.

3. Coarctation of the aorta caused significant changes in diastolic and systolic LV function. Remodeling and growth of the CoA segment took place months after repair, and after repair, the RV size and the velocity time integrals of mitral inflow increased. Serum levels of natriuretic peptides decreased during follow-up after repair and they correlated with echocardiographic findings. Close follow-up is thus needed despite cessation of LV pressure overload, since LV hypertrophy and hyperkinesia did persist even in normotensive patients, along with growth of the coarctation segment.

4. A significant proportion of children with Mulibrey nanism suffered from myocardial restriction and impairment of LV function. In symptomatic patients, serum levels of proBNP were higher and cardiac systolic function was more deteriorated than in asymptomatic patients. Significant correlations appeared between indices of LV function, size of the left atrium, and levels of natriuretic peptides, indicating that measurement of serum levels of natriuretic peptides can be used in the clinical follow-up of this patient group despite its dependence on loading conditions.

5. By serum levels of natriuretic peptides, it was possible to monitor the effect of intervention on the hemodynamic loading condition. In right and left ventricular volume overload, left ventricular pressure overload, and in patients with Mulibrey nanism, levels of natriuretic peptides were higher than in control patients. After cessation of abnormal loading, the levels decreased to those of controls within 6 months in patients with PDA and in those with CoA. In patients with ASD, these levels remained higher than in controls several years after closure of the defect. Serum levels of natriuretic peptides correlated with echocardiographic measurements. Peptides can thus be helpful in clinical decision-making regarding medical treatment and surgical and percutaneous interventions.

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ORIGINAL PUBLICATIONS (I-IV)

I. Eerola A, Pihkala JI, Boldt T, Mattila IP, Poutanen T, Jokinen E: Hemodynamic improvement is faster after percutaneous ASD closure than after surgery. *Catheter Cardiovasc Interv.* 69:432-41, 2007.

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